INVESTIGATION OF CROSSTALK BETWEEN WNT AND HEDGEHOG SIGNALING PATHWAYS

by

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ABSTRACT

INVESTIGATION OF CROSSTALK BETWEEN WNT AND HEDGEHOG SIGNALING PATHWAYS

In the last few years, an intense interest is being shown in the evolutionarily conserved signaling pathways which have crucial roles during embryonic development. The most intriguing factor behind this interest is that malfunctioning of these signaling pathways (Hedgehog, Notch, Wnt etc.) leads to several human diseases, especially to cancer. Furthermore, these signaling pathways are not isolated highways, contrarily they interact with each other in a number of ways. This study deals with the β-catenin dependent branch of Wnt signaling and the Hedgehog signaling pathways which offer potential targeting points for cancer drug development. Here, through integration of protein-protein interaction data and Gene Ontology annotations, the Wnt/β-catenin and Hedgehog signaling networks consisting of proteins with statistically high probability of being biologically related to these signaling pathways were reconstructed in *D. melanogaster*. The reconstructed networks have scale-free topologies like most of the other biological networks. Furthermore, the linear paths which mediate the signal from the input proteins to the output proteins were identified in these reconstructed networks using interacting proteins. The receptors (fz2 for the Wnt ligand and ptc for the Hedgehog ligand) were found to be involved in the linear paths with the highest participations following the input and output proteins for both Wnt and Hedgehog signaling networks. Lastly, the identification of 477 common proteins between the reconstructed Wnt/β-catenin (656 proteins) and Hedgehog signaling (568 proteins) networks revealed that these two signaling networks interact with each other. The identification of regulatory proteins functioning in these signaling networks is crucial toward efforts for preventing tumour formation. The proteins arm, frizzled receptors (fz and fz2), arr, Apc, Axn, ci and ptc, which have been reported as potential drug targets in the literature, were also detected as essential proteins in these networks.

ÖZET

WNT VE HEDGEHOG SİNYAL İLETİ YOLLARININ BİRBİRLERİYLE OLAN ETKİLEŞİMLERİNİN İNCELENMESİ

Son yıllarda, embriyonik gelişimde önemli role sahip evrimsel açıdan korunmuş sinyal ileti yolları yoğun bir ilgi görmektedir. Bu ilginin arkasındaki en önemli faktör, sinyal ileti yollarındaki (Hedgehog, Notch, Wnt vb.) herhangi bir işlev bozukluğunun insanda çeşitli hastalıklara, özellikle de kansere sebep olmasıdır. Ayrıca, bu sinyal ileti yolları izole sistemler olmayıp, aksine birbirleriyle etkileşim halindedirler. Bu çalışmada, her biri kanser tedavisi sürecinde tedaviye ilişkin yeni yaklaşımlar açısından önem arzeden Wnt/β-katenin ve Hedgehog sinyal ileti yolları incelenmiştir. Protein-protein etkileşimleri ve Gen Ontolojisi ifadelerinin bütünleştirilmesi yoluyla, *D.melanogaster* (meyve sineği) organizmasında Wnt/β-katenin ve Hedgehog sinyal ileti ağyapıları yeniden kurulmuştur. Bu yöntem, kurulan sinyal ileti ağyapılarına biyolojik açıdan Wnt/β-katenin ve Hedgehog sinyal ileti yollarında olma olasılığı yüksek proteinlerin dahil edilmesini sağlamıştır. Oluşturulan ağyapılarının boyuttan bağımsız bir topoloji ile küçük dünya özelliklerine sahip olduğu görülmüştür. Bunun yanısıra, ağyapı içerisindeki giriş proteininden başlayıp çıkış proteininde sonlanan tüm doğrusal yolizleri bulunmuştur. Reseptör proteinlerinin (wnt ligandının reseptörü fz2, hedgehog ligandının reseptörü ptc) doğrusal yolizlerinde giriş ve çıkış proteinlerinden sonra en yüksek katılım yüzdesine sahip olduğu saptanmıştır. Kurulan Wnt/β-katenin (656 protein) ve Hedgehog (568 protein) sinyal ileti ağyapılarının her ikisinde de görev alan 477 adet ortak proteinin tespit edilmesi, bu iki sinyal ileti yollarının birbiri ile etkileşim halinde olduğunu ortaya koymaktadır. Bu karmaşık sinyal ileti yollarındaki düzenleyici proteinlerin tespiti, sinyal iletim ağlarındaki aksaklığın sebep olduğu tümör oluşumlarının engellenmesi açısından önem teşkil etmektedir. Literatürde potansiyel ilaç hedefi olarak gösterilen arm, frizzled reseptörleri (fz ve fz2), arr, Apc, Axn, ci, ve ptc proteinleri, aynı zamanda kurulan Wnt/β-katenin ve Hedgehog sinyal ileti ağyapılarında temel proteinler olarak tespit edilmiştir.

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1. INTRODUCTION

Signaling provides the communication of living cells among each other by processing biological information. The signals arrive at the surface of target cells by signaling molecules, where they bind to their receptors and activate signaling mechanisms leading to effects such as proliferation, differentiation, or migration (Ching and Nusse, 2006). Recently, a variety of diseases has been explained by abnormality of signal transduction pathways. The Wnt signaling pathway and the Hedgehog signaling pathway are known to be involved in embryonic development and growth, and their disregulation has been reported to lead to various kinds of human cancers such as pancreatic, lung, breast, colon, prostate, and colorectal cancers (Maeda *et al*., 2006). Wnt signaling pathway is known to branch between β-catenin dependent and β-catenin independent pathways. The best characterized and understood among them is the Wnt/β-catenin pathway, often called the "canonical" Wnt pathway. Characterization of the canonical Wnt and Hedgehog signaling networks is central for determination of the strategies to target these pathways in cancer drug discovery.

Most of the research published so far has reported experimental and computational work to elucidate small-scale mechanisms around key proteins in Wnt and Hedgehog signaling (Jacob and Lum, 2007; DasGupta *et al*., 2005b; Siegfried *et al*., 1994). However, generating the global picture of Wnt and Hedgehog signaling is very important in order to understand the mechanisms at healthy (development and growth) as well as diseased (cancer) states. This fact necessitated the reconstruction of Wnt/β-catenin and Hedgehog signaling protein-protein interaction networks. The organism, *Drosophila melanogaster*, was preferred here to reconstruct the networks, since much of the current understanding of Wnt and Hedgehog signaling mechanisms comes from studies conducted in *D. melanogaster*.

After introducing the goals of this thesis, the following chapter concentrates on the theoretical background and the insights on cell signaling, especially Wnt and Hedgehog signaling and their impact on cancer. The third chapter focuses on the methods of

reconstruction and computational analysis of the Wnt and Hedgehog signaling networks. In this study, the interactome data was integrated with GO annotations for reconstruction of large scale protein interaction networks which are composed of candidate proteins related to canonical Wnt and Hedgehog signaling in *D. melanogaster*. The structural analyses of the reconstructed networks were then performed. First, graph theoretic analysis was used to determine the graph properties of the reconstructed networks as well as to detect the proteins that are well or poorly connected in the interaction networks. The reconstructed Wnt and Hedgehog signaling networks were then decomposed into linear paths from inputs (i.e. ligands) to outputs (i.e. transcription factors) to obtain detailed information about the signaling mechanisms. Furthermore, the modules in the networks were detected and the crosstalk analysis between the networks was performed. The fourth chapter gives the results of reconstruction and analyses of the Wnt and Hedgehog signaling networks. Finally, the thesis is concluded with the summary of the main points and some recommendations (fifth chapter) for further studies.

This study provides a comprehensive understanding of Wnt/β-catenin and Hedgehog signaling networks with the indication of essential components, and also proves that signaling networks are not isolated; rather they interact with each other and form complex signaling networks.

2. BACKGROUND ASPECTS

2.1. Cell Signaling

All cells make decisions on the basis of the sensation carried from their surrounding environment. Cells in multi-cellular organisms must recognize the presence of neighboring cells and hormones when making decisions such as to multiply, move or die. These processes require the transfer of biological information between the cells. Signal transduction is the study of the mechanisms by which this transfer of biological information takes place. Signaling pathways play crucial roles in development and growth such as tissue homeostasis and regeneration. Too much or too little activity from a signaling pathway can cause serious results such as developmental defects or, later in life, disease. Therefore, it can be hoped that in-depth characterization of signaling pathways will lead eventually to an ability to intervene in diseases in which those pathways are defective and define related signaling molecules as drug targets (Downward, 2001; Gordon and Nusse, 2006).

Cell signaling encompasses the generation and transmission of a signal, the reception of the signal and the propagation of that signal within the cell. Signal transmission is initiated by an extracellular molecule, ligand. The signal is received by the cell, when the ligand binds to the receptor in a specific manner (Nelson, 2008). Then, a cascade of intracellular signaling proteins transmits the signal to the target proteins and finally leads to a response (Fig. 2.1). The response may be the alteration of metabolism if the target protein is a metabolic enzyme. On the other hand, if the target protein functions as a transcriptional regulator, the response may be changes in gene expression. Also, the signal may be transmitted to a cytoskeletal protein, which alters the shape or location of the cell.

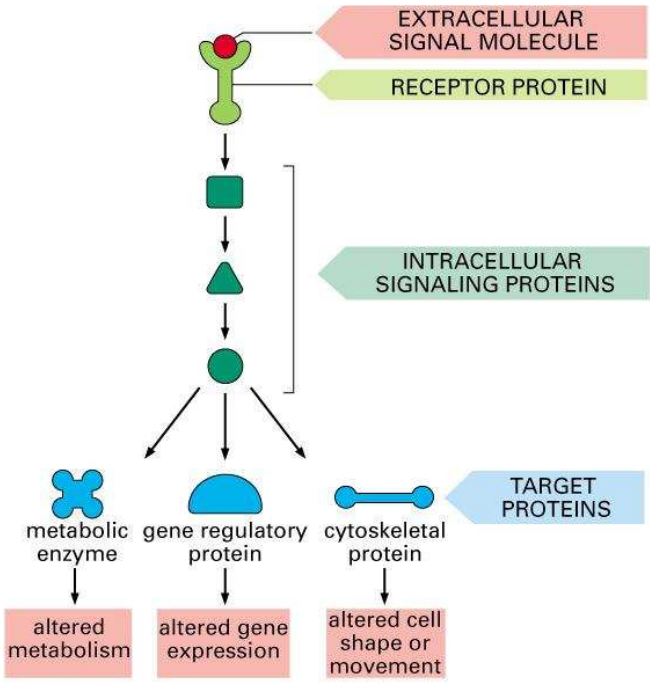


Figure 2.1. Simplified view of an intracellular signaling pathway (Alberts *et al.*, 2002)

2.2. Wnt Signaling

The Wnt signaling pathway is one of the most important pathways that regulate growth, survival, proliferation, migration and differentiation. Strict regulation of the Wnt signaling pathway is critical, since insufficient or excess activity of it results in severe developmental defects or, later in life, cancer (Vincan, 2008). Therefore, many components of this signaling pathway may serve as rational targets for cancer drug development.

The term "Wnt" was derived from a combination of the Drosophila segment polarity gene *Wingless* and the mouse proto-oncogene *Int-1* (Paul and Dey, 2008; Vincan, 2008). Wnt proteins are secreted glycoproteins including a signal peptide for secretion, many potential glycosylation sites and multiple cysteine residues responsible for ensuring proper folding and secretion (Ishikawa, 2005; Vincan, 2008). At least 19 Wnt members are known in human, 7 in fly and 5 in *C.elegans* (Nusse, 2005).

Up to now, three major pathways which are transduced by Wnt signals have been studied. The best characterized and understood pathway is the Wnt/β-catenin pathway, often called the "canonical" Wnt pathway. Then, others called "non-canonical" Wnt

pathways are the planar cell polarity (PCP) pathway and the Wnt-calcium (Wnt/Ca^{2+}) pathway which are β-catenin-independent processes (Vincan, 2008; Maiese *et al*., 2008; Wang and Boris, 2004). All Wnt signaling pathways are initiated by the interaction of Wnt proteins with Frizzled (FZD) receptors and followed by the activation of the cytoplasmic effector Dishevelled (DSH).

The schematic representation of the Wnt/β-catenin and the two noncanonical pathways is illustrated in Figure 2.2. In the Planar Cell Polarity pathway, upon interaction of a Wnt ligand with a Frizzled receptor and activation of the cytoplasmic protein Dishevelled, the signal is transduced through two distinct small G proteins Rho and Rac, which convey cell polarity via their respective effectors ROCK and JNK. In the Wnt/Ca^{2+} pathway, following the activation of the Dishevelled, the activation of the key component PLC and an increase in intracellular calcium levels induces activation of the calcium-sensitive proteins Calcinerium, CamKII, and PKC (Pandur, 2005; Vincan, 2008). While the cell polarity pathway has functions in establishing cell polarity, the Wnt/Ca^{2+} pathway mediates cytoskeletal dynamics and cell adhesion, through the regulation of intracellular calcium levels (Vincan, 2008). In the present study the canonical Wnt/β-catenin cascade is investigated.

2.2.1. Wnt/β-catenin Signaling Mechanism: An Overview

The ultimate outcome of Wnt/β-catenin pathway activation is the formation of cytoplasmic pool of free β-catenin in the cell that enters the nucleus and forms a complex with members of the LEF/TCF family of transcription factors to regulate the expression of the target genes. This is accomplished by controlling the stability of β-catenin. In the absence of Wnt ligands, β-catenin is degraded by the proteasome pathway, keeping the levels of free β-catenin low (DasGupta *et al*., 2005a).

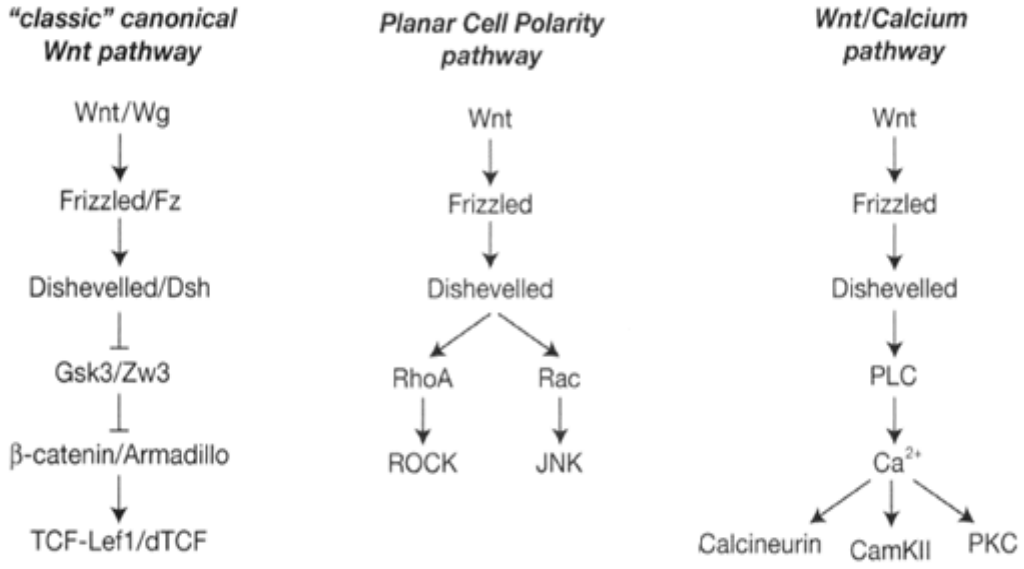


Figure 2.2. Schematic representation of the classic canonical and two most studied non-canonical pathways (Vincan, 2008).

Wnt/β-catenin signaling pathway starts when Wnt proteins bind to a cell surface frizzled (FZD) receptor and its coreceptor LDL receptor-related protein 5/6 (LRP5/6), leading to the activation of a dishevelled protein family member (DSH). Active DSH inhibits a complex consisting of glycogen synthase kinase 3β (GSK3β), Axin (AXIN), casein kinase (CKI) and adenomatous polyposis coli (APC). In its active state, this complex induces the phosphorylation of β-catenin via GSK3β and CKI. The phosphorylation of β-catenin targets it for ubiquitination by β-TrCP resulting in the proteosomol degradation of β-catenin. The inhibition of the destruction complex prevents phosphorylation, hence degradation of β-catenin does not take place. It accumulates in the cytoplasm and translocates into the nucleus, where it binds and activates a member of the T-cell factor (TCF)/lymphoid enhancer binding factor (LEF) transcription factor family (Figure 2.3). This leads to the expression of the target genes, which are involved in the regulation of cellular processes, such as proliferation and differentiation (Gehrke *et al*., 2009; Salinas, 2007; Paul and Dey, 2008).

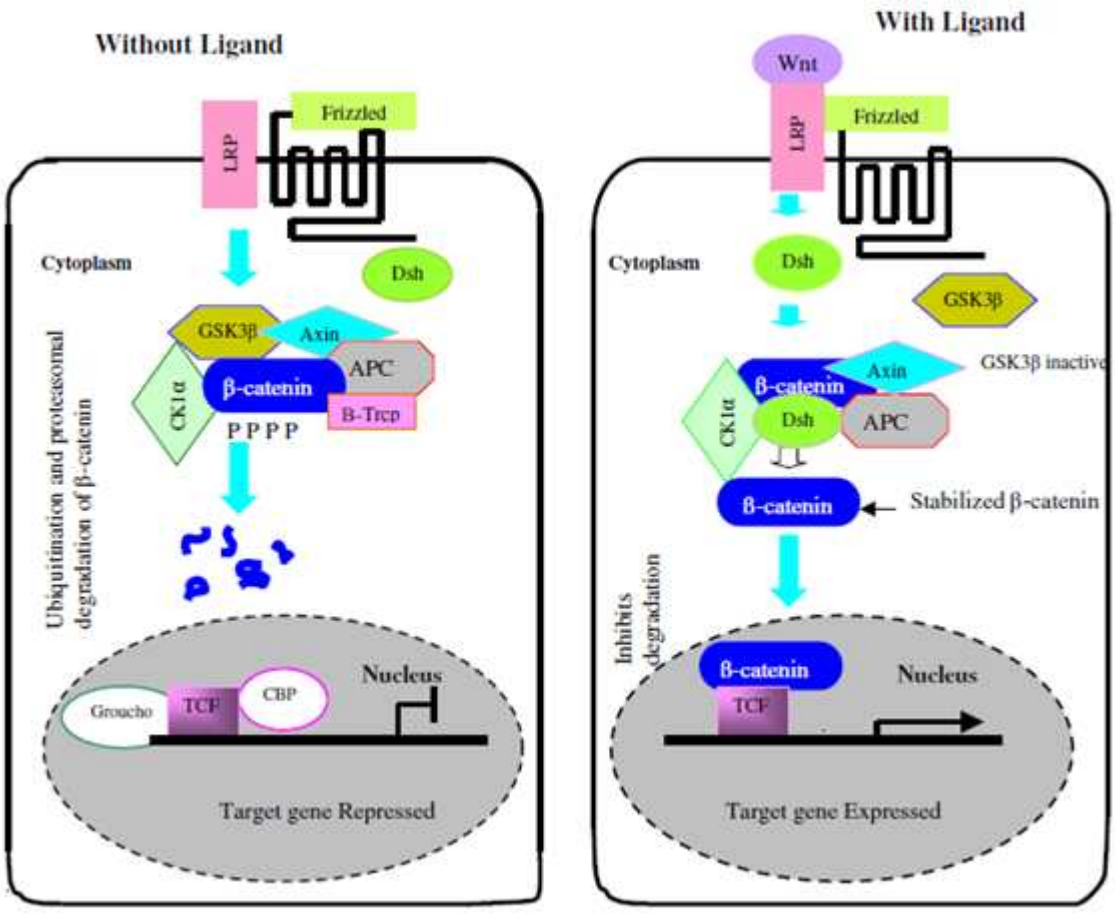


Figure 2.3. The overview of the canonical Wnt signaling pathway (Paul and Dey, 2008).

2.2.2. Wnt/β-catenin Signaling Pathway in *D. melanogaster*

D. melanogaster has long been an important model organism in genetics due to its small size and quick generation time, which makes even large numbers of them relatively easy to maintain and observe in the laboratory. Much of the current understanding of Wnt (also known as Wingless in *Drosophila*) signaling mechanisms comes from studies conducted in *D. melanogaster*. Wnt signaling is highly significant during normal development and patterning of *Drosophila*. The developmental roles of Wnt signaling include patterning of embryonic segmentation cascade, wings, legs, eyes, heart and muscles (Arias, 2008; Vincan, 2008).

Considerable body of work shows that the canonical Wnt signaling pathway is similar in vertebrates and *D.melanogaster*. Like in vertebrates, the main intracellular outcome of the canonical Wnt pathway in *D.melanogaster* is the stabilization of the

Armadillo (Arm, the *Drosophila* homolog of β-catenin) in the cytoplasm, which is otherwise degraded by a complex comprised of Axin, zeste white 3 (Zw3 or shaggy (Sgg), the *Drosophila* homolog of glycogen synthase kinase-3β), APC and casein kinase-I. Upon the binding of the *Drosophila* Wnt1 homolog Wingless (Wg) to its receptor, frizzled (Fz), stabilized Arm translocates to the nucleus, where together with Pan (a transcription factor of the TCF/LEF family), it activates downstream target genes (DasGupta *et al*., 2005a; DasGupta *et al*., 2005b; Vincan, 2008).

2.2.3. Wnt/β-catenin Signaling as Cancer Drug Targets

Wnt and a handful of other signaling systems have important roles in regulating the development, whereas in cancer and other diseases they lose this control. For example, when a signaling component experiences a gain-of-function mutation or an elevated activity it might become an oncogene. Alternatively, if an inhibitor undergoes a loss-of-function mutation or reduced activity it does not function as a tumour supressor any more. These changes in Wnt/β-catenin signalling pathway components have been linked to several type of cancer (Table 2.1). Besides cancer, Alzheimer disease, osteoarthritis, tooth development and diseases of the bone, eye and heart are other proliferative diseases arised from the altered function of the components of the Wnt/β-catenin pathway. That is why cancer researches and pharmacologists show considerable interest in this signaling pathway. (Klaus and Birchmeier, 2008; Paul and Dey, 2008).

The identification of the important regulatory proteins and their functions in the signaling pathway determines the strategies to target this pathway in cancer drug discovery. Below, the existing drug design strategies for the Wnt/β-catenin signaling pathway in cancer are summarized.

Over 90% of colon cancers and a high percentage of other cancers originate from the mutations in the Wnt pathway which creates continous transcription of many target genes supporting cell proliferation. Many studies concerning the cell culture reveal that inhibition of the Wnt pathway can normalize cancer cells. Therefore, it is likely that inhibiting the Wnt pathway could make a great contribution to cures for cancer (Klaus and Birchmeier, 2008). As previously described, the initial step in Wnt/β-catenin signaling is

the interaction between Wnt and Fzd. So, if the binding of Wnt ligand to its Fzd receptor is inhibited selectively by an agent, cancer cell growth can be inhibited. The major drawback of this strategy is that not much is known about the ligand-receptor interaction in Wnt signaling pathway. Alternatively, the overexpression of natural inhibitors of Wnt signaling in vertebrates such as sFRPs, WIF-1 or DKK could be used as an approach in cancer therapy (Janssens *et al*., 2006; Luu *et al*., 2004).

The multiprotein β-catenin destruction complex could be a relatively good drug target. Among the components of the destruction complex, GSK3β is the best validated target and activation of it results in the inhibition of the Wnt signalling pathway. For instance, the differentiation-inducing factors (DIFs) inhibit Wnt/ β-catenin signaling pathway by activating GSK3β, so they are strong candidates for new anticancer drugs (Janssens *et al*., 2006; Yanaga and Sasaguri, 2009).

Since aberrant Wnt signaling results in increased β-catenin levels, directly targeting β-catenin seems to be a rational approach. Several strategies have been used while targeting β-catenin such as antisense, RNA interference and protein knockdown strategies (Luu *et al*., 2004). Furthermore, inhibition of β-catenin/Tcf4 complex is another strategy that can be used to inhibit Wnt signaling pathway, but the inhibitor must selectively interfere with the complex without disrupting other fundamental interactions of β-catenin (Janssens *et al*., 2006; Gehrke *et al*., 2009).

2.3. Hedgehog Signaling

Hedgehog (Hh) is a secreted protein that has a crucial role in the growth, patterning, and morphogenesis during embryonic development in both vertebrates and invertebrates. Aberrations in the Hedgehog signaling pathway can lead to devastating developmental disorders and cancer. Therefore, a better understanding of the Hedgehog signaling pathway is indispensable to provide new therapies for Hedgehog related disorders (Ayers *et al*., 2009).

Table 2.1. Wnt/β-catenin signaling pathway components involved in cancer

Gene	Cancer type	Mutation or activity change	References
Wnt(s)	Breast, melanoma, carcinogenesis	Elevated	(Paul and Dey, 2008; Janssens *et al*., 2006)
sFRP(s)	Colon, mesothelioma	Reduced	(Paul and Dey,2008; Gehrke *et al*., 2009)
WIF-1	Colorectal cancer	Reduced	(Vincan and Barker, 2008; Janssens *et al*., 2006; Gehrke *et al*., 2009)
LRP5	Osteosarcoma, thyroid tumours	Elevated	(Klaus and Birchmeier, 2008; Janssens *et al*., 2006)
Fzd(s)	Carcinogenesis	Elevated/overexpression	(Klaus and Birchmeier, 2008; Janssens *et al*., 2006)
β-catenin	Colorectal cancer, melanoma, gastric cancer, prostate cancer, ovarian cancer, hepatocellular carcinoma, hepatoblastoma, Wilm's tumor.	Gain of function	(Luu *et. al*., 2004; Giles *et al.*, 2003; Janssens *et al*., 2006)
APC	FAP, colorectal cancer, melanoma	Loss of function/reduced	(Klaus and Birchmeier, 2008; Janssens *et al*., 2006; Vincan and Barker, 2008)
Axin	Colon, ovarian carcinoma	Loss of function	(Klaus and Birchmeier, 2008; Janssens *et al*, 2006; Giles *et al*., 2003)
GSK3β	Colorectal cancer	Deregulated	(Shakoori *et al*.,2005; Janssens *et al*., 2006)

APC: adenomatous polyposis coli; Fzd: Frizzled; GSK3β: glycogen synthase kinase 3β; LRP: LDL-receptor-related protein; sFRP: secreted Frizzled related protein; WIF: Wnt inhibitory factor.

Hedgehog protein is synthesized as a precursor and undergoes an autocatalytic reaction to be a fully active signaling molecule. First, the C-terminal domain is removed and a cholesterol molecule is attached to the C-terminus of the processed Hh protein. Next, another cholesterol molecule is attached to the N-terminus of Hh in a process mediated by Skinny hedgehog (Ski) and for the release of the dually lipidated Hh from the cell membrane Dispatched (Disp), a 12-transmembrane protein is required (Varjosalo and Taipele, 2007). Mammals have three Hh forms: Sonic (Shh), Indian and Desert, but Shh

has the greatest scope of activity. The three vertebrate Gli transcription factors, Gli1, Gli2, Gli3 and their fly homolog Cubitus interruptus (Ci), are associated with the Hedgehog pathway. The regulation of the Hedgehog pathway can be described as two state models; in the absence or presence of Hh. In the absence of hh, Ci is modified to its repressor form. On the contrary, upon Hh reception in the cell Ci is processed into an activator leading to target gene activation (Mullor *et al*., 2002; Horabin, 2007).

Several components of the Hedgehog pathway were first identified in *Drosophila* and later described in vertebrates (Mullor *et al*., 2002). In *Drosophila*, Hedgehog signaling is necessary for proper patterning of the embryo and multiple adult structures (Ogden *et al*., 2004).

2.3.1. Hedgehog Signaling Pathway in *D. melanogaster*

In *Drosophila*, the ultimate target of the Hedgehog pathway is the regulation of the transcription factor Cubitus interruptus (Ci). The response to Hh is mediated by Ci, a zinc finger transcription factor. Depending on the presence or absence of the Hh ligand, Ci is processed into either an activator or repressor. These fates are regulated by two membrane proteins, Patched (Ptc), a 12-transmembrane protein receptor with a sterol sensing domain, and Smoothened (Smo), a 7-transmembrane protein related to the Frizzled family of G-Protein Coupled Receptors (GPCR). Ptc acts as an inhibitor of Smo and downstream of Smo, there is a multi-protein complex known as the Hedgehog cytoplasmic complex, which comprises the Cubitus interruptus (Ci), the serine/threonine kinase Fused (Fu), the kinesin-related microtubule binding protein Costal 2 (Cos2) and the protein Supressor of fused (Sufu). Cos2 is also used as a scaffold by the protein kinase A (PKA), casein kinase (CKI) and glycogen synthase kinase 3 (GSK3). These kinases promote the processing of Ci to the repressor form, with the activity of the F-box protein, Slimb (Slmb), a component of the SCF ubiquitin ligase complex (Horabin, 2007; Varjosalo and Taipale, 2007).

In Figure 2.4, a simplified depiction of Hedgehog signaling is illustrated. In the absence of Hedgehog (Hh), Ptc represses Smo and this triggers the events that lead to the proteolysis of Ci to its repressor form which enters the nucleus and inhibits Hedgehog target gene expression. In the presence of Hh, the inhibitory effects of Ptc on Smo are

released. PKA, CKI and GSK3 are relieved from Cos2, preventing the proteolysis of Ci. This converts Ci from a transcriptional repressor to an activator form, which enters the nucleus to induce the transcription of Hedgehog target genes such as *patched* (*ptc*), *decapentaplegic* (*dpp*) and *engrailed* (*en*) (Horabin, 2007; Zhang *et al*., 2005).

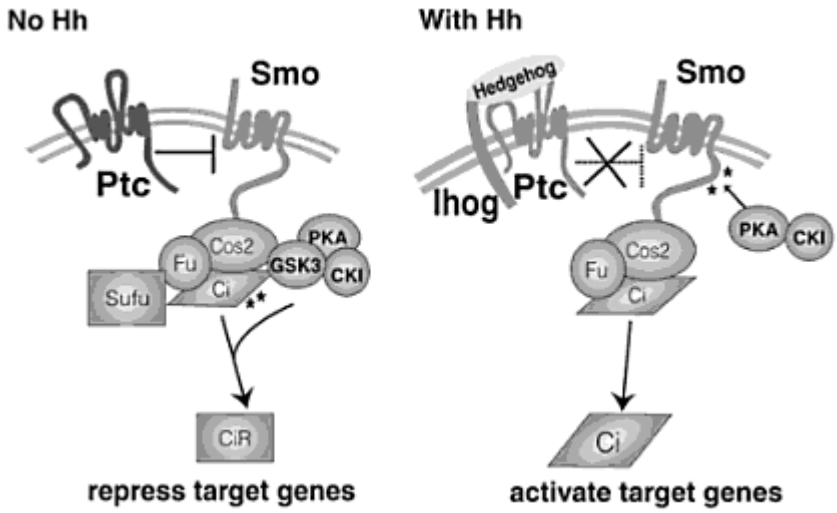


Figure 2.4. Simplified depiction of Hedgehog signaling (Horabin, 2007)

2.3.2. Hedgehog Signaling as Cancer Drug Targets

The Hedgehog signaling pathway regulates the development of multiple tissues during embryonic development, and contributes to tissue homeostasis in adults. Misregulation in Hh signaling pathway activity has been observed in many type of human disorders, including cancer. Hedgehog signaling pathway was strongly linked to cancer when the Hedgehog receptor Ptc was identified as a tumour suppressor gene that has crucial roles in the human nevoid basal cell carcinoma syndrome (NBCCS). Excessive Hedgehog signaling has been found in several types of cancer including pancreatic cancer, lung cancer, breast cancer, prostate and gastrointestinal cancer (Gialmanidis *et al*., 2009; Toftgard, 2000). Therefore, Hh pathway is an important and novel therapeutic target in drug development.

Recent studies have revealed that mutations in the *smoothened* (*smo*) gene and loss-of-function mutations in the *patched* gene cause pancreatic tumors. It was demonstrated that cyclopamine, a steroidal alkaloid, blocks the Hh pathway by antagonizing Smo. This

indicates that Hh pathway may be a therapeutic target for pancreatic cancer (Xu *et al*., 2009).

Another study indicated that Hedgehog signaling pathway is extensively activated in non-small cell lung carcinomas (NSCLC). Shh (Sonic hedgehog) overexpression and mutations of Ptc, Smo and Su(fu) have been involved in activation of Hedgehog signaling in NSCLC (Gialmanidis *et al*., 2009).

Furthermore, Kubo and coworkers (2004) revealed that Hedgehog pathway is constitutively activated in most breast carcinomas. The overexpression of Shh and Gli1 were observed in certain breast cancer cell lines and the cyclopamine has been used to suppress the expression of Gli1 and the growth of the Hedgehog pathway-activated breast carcinoma cells. Therefore, inhibition of the Hedgehog pathway may be an important strategy at the treatment of patients with breast carcinoma (Kubo *et al*., 2004; Kasper *et al*., 2009).

Table 2.2. Hedgehog signaling pathway components involved in cancer

Gene	**Cancer type**	**Mutation or activity change causing cancer**	**References**
Gli1	Breast cancer	Overexpression	(Kubo *et al*., 2004; Kasper *et al*., 2009)
Ptch1	BCC, pancreatic cancer, medulloblastoma	Inactivating mutations	(Toftgard, 2000; Xu *et al*., 2009; Rubin and Sauvage, 2006)
Shh	Breast cancer, NSCLC, pancreatic cancer	Overexpression	(Kasper *et al*., 2009; Gialmanidis *et al*., 2009; Sheng *et al*., 2004)
Smo	BCC, NSCLC	Overexpression	(Saldanha, 2001; Gialmanidis *et al*., 2009)
Su(fu)	Prostate cancer	Reduced activity	(Sheng *et al*., 2004)

Ptch: patched; Shh: sonic hedgehog; Smo: smoothened; Su(fu): supressor of fused; BCC: basal cell carcinoma; NSCLC: non-small cell lung carcinomas.

2.4. Reconstruction of Signaling Networks

Signaling networks are the communication networks that connect cellular components and coordinate the phenotypic response. To understand how a signalling network generate a specific phenotype, it is essential to construct a model of the signaling network so that hypotheses can be verified, rejected or modified (Hyduke and Palsson, 2010).

A network reconstruction includes a chemically accurate representation of all of the biochemical events that are occurring within a defined signaling network, and incorporates the interconnectivity and functional relationships that are inferred from experimental data. Network reconstructions provide the framework for the application of mathematical methods that can quantitatively describe the properties of signaling networks. Network reconstruction involves the integration of several sources of data to describe the biochemical transformations that occur in a given network. Contextual specificity is a crucial consideration in answering five questions for signaling network reconstruction: What proteins and other network components participate? What are the ligand-receptor interactions? What are the receptor-intracellular component interactions? What are the intracellular component interactions? What are the intracellular component-DNA interactions? Genome annotation, biochemical experimentation, cell-physiology characterizations, expression arrays, and other such data sources each provide different types of datum that answer these questions and contribute to the reconstruction of a given cellular signaling network (Papin *et al.*, 2005).

Signaling network reconstruction can be performed in three different ways (Figure 2.5). The first approach consists of reconstructions of highly connected nodes in networks. In this method, the compounds and reactions that are associated with a given protein, ion or metabolite are comprehensively listed. The second approach in network reconstruction involves forming linear pathways that connect signaling inputs to signaling outputs. For example, such a pathway might be the delineation of all of the steps from the binding of a growth factor to its receptor through the subsequent activation of a transcription factor that induces the expression of target genes. The third approach consists of identifying signaling

modules. Such modules historically consist of groups of compounds and proteins that function together under certain conditions (Papin *et al.*, 2005).

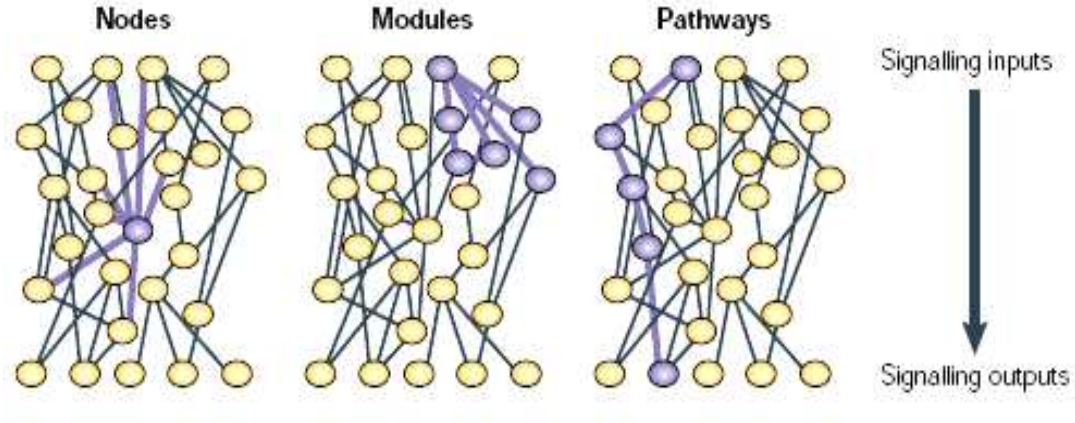


Figure 2.5. Approaches in reconstruction of signaling networks (Papin *et al.*, 2005)

Large-scale signaling networks are complex. Their complexity necessitates the use of methods from systems sciences, which are quite mathematical to understand the network properties of cellular signaling. Structural and dynamic analyses measure the time-invariant/topological and the time-variant properties of a network, respectively (Papin *et al.*, 2005).

Structural analyses can identify components that are well or poorly connected (and therefore of potential interest for drug targeting). For example, the green component is the most highly connected in the schematic of a signaling network (Figure 2.6), and so drugs that inhibit the activity of this hypothetical component could have the broadest effect on the functions of the network. Structural analyses can also characterize which signaling inputs generate which signaling outputs. For example, in the schematic of signaling network (Figure 2.6) the signaling inputs 1 and 4 can generate signaling outputs 2, 3 and 5.

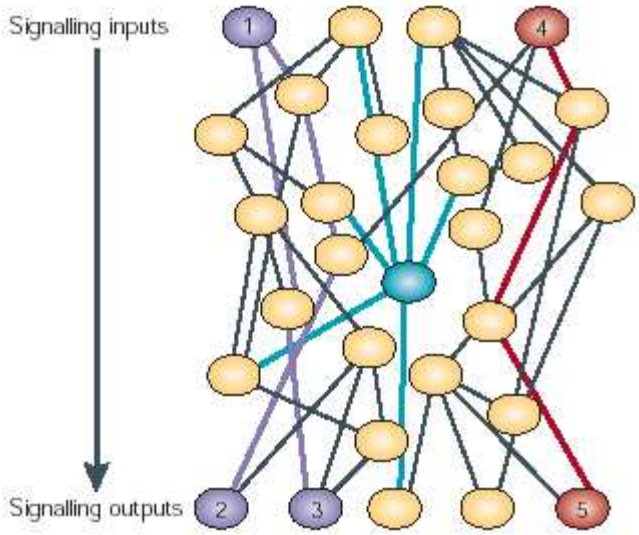


Figure 2.6. Structural analyses of signaling networks (Papin *et al.*, 2005)

3. MATERIALS AND METHODS

The reconstruction and analysis of Wnt and Hedgehog signaling networks are based on the systems biology approach which incorporates several types of biological data and numerous analysis techniques.

3.1. Data

3.1.1. Protein-Protein Interaction (Interactome) Data Sources

DroID is a comprehensive protein interactions database (Yu *et al*., 2008) designed specifically for the model organism *D. melanogaster*. The Drosophila Interactions Database (DroID) includes published physical protein interactions, genetic interactions, and computationally predicted interactions. All of the data in DroID can be accessed and downloaded freely from DroID home page, http://www.droidb.org.

Interaction data in DroID is mostly obtained from large-scale screens and also from small-scale 'low throughput' experiments collected by manual curation of the literature. The current version of DroID (v5.0) contains 144352 total interactions among 9524 *D. melanogaster* genes. Furthermore, it houses 26123 physical interactions among 7640 genes (Yu *et al*., 2008).

Three public databases, BioGRID (Stark *et al*., 2006), DIP (Salwinski *et al*., 2004) and MINT (Chatr-aryamontri *et al*., 2007) also provide protein interactions for many different species. The major drawback of these multi-species databases is that they are not fully comprehensive for any organism (Yu *et al*., 2008).

3.1.2. Sequence Data Sources

Universal Protein Resource (UniProt), freely accessible at http://www.uniprot.org, provides inclusive and excellent resource on protein sequence and functional information. UniProt has four databases for different aims. The UniProt Knowledgebase (UniProtKB)

contains comprehensive functional information on proteins. The Uniprot Archieve (UniParc) is a repository containing most of the publicly available protein sequences in the world. UniProt Reference Clusters (UniRef) integrates the sets of sequences according to identity for fast searches and lastly the UniProt Metagenomic and Environmental Sequences (UniMES) is a database developed for metagenomic and environmental data (The UniProt Consortium, 2010).

In addition to main data for each protein (the amino acid sequence, protein name or description etc.), UniProtKB provides annotation information such as biological ontologies and domain information. UniProtKB consists of two sections: UniProtKB/Swiss-Prot and UniProtKB/TrEMBL. UniProtKB/Swiss-Prot contains manually-annotated records with information extracted from literature and curator-evaluated computational analysis. On the contrary, UniProtKB/TrEMBL includes only computationally analyzed records (The UniProt Consortium, 2010).

3.1.3. Gene Ontology Annotations

The Gene Ontology (GO) project provided consistent vocabulary for describing the roles of genes and gene products given in databases belonging to many organisms. Cellular component, biological process and molecular function are three ontologies developed by the GO Consortium and are freely available at http://www.geneontology.org (The Gene Ontology Consortium, 2000).

Cellular component refers to the place in the cell where a gene product is active. Biological process is defined as biological objective that the gene or gene product contributes and molecular function refers to the biochemical activity of a gene product (The Gene Ontology Consortium, 2000).

3.2. Data Visualization

Computer-aided models to construct biological networks are a keystone for systems biology approach. Cytoscape, which is a free software package (http://www.cytoscape.org) for visualizing, modeling and analyzing biomolecular interaction networks, is one of these

models and used here for drawing the network. The features of Cytoscape are enriched via implementing several plugins having different missions (Shannon et al., 2003). NetworkAnalyzer (Assenov *et al*., 2008), MCODE (Bader *et al*., 2003) and BiNGO (Maere *et al*., 2005), used in the present study, are three freely available plugins implemented to Cytoscape. They will be described in detail in section 3.3 under 'Methods'.

3.3. Methods

In this work, in addition to the reconstruction of Wnt and Hedgehog signaling networks in *D. melanogaster*, the following analyses were performed: sequence similarity analysis, graph theoretical analysis, network decomposition analysis, module analysis and crosstalk analysis.

3.3.1. Network Reconstruction by GO Annotations

In the present study, as illustrated in Figure 3.1, the reconstruction of Wnt and Hedgehog signaling networks in *D. melanogaster* was performed by integrating protein-protein interaction data and Gene Ontology (GO) annotations. The input to the algorithm is the core proteins known to have certain functions in Wnt or Hedgehog signaling pathways. In the first step, GO annotations (cellular component, molecular function and biological process) of the core proteins are collected to form an annotation collection table (Appendix A). Next, all the *D. melanogaster* proteins and their GO annotations are obtained from the file gene_association.fb.gz which can be downloaded from Gene Ontology website (http://www.geneontology.org/GO.current.annotations.shtml). Then, *D. melanogaster* proteins whose all three GO terms match with those in the annotation collection table are accepted to the network. As a final step, to reconstruct the network, the physical protein interaction data are obtained from DroID, a comprehensive protein interactions database designed specifically for *D. melanogaster.*

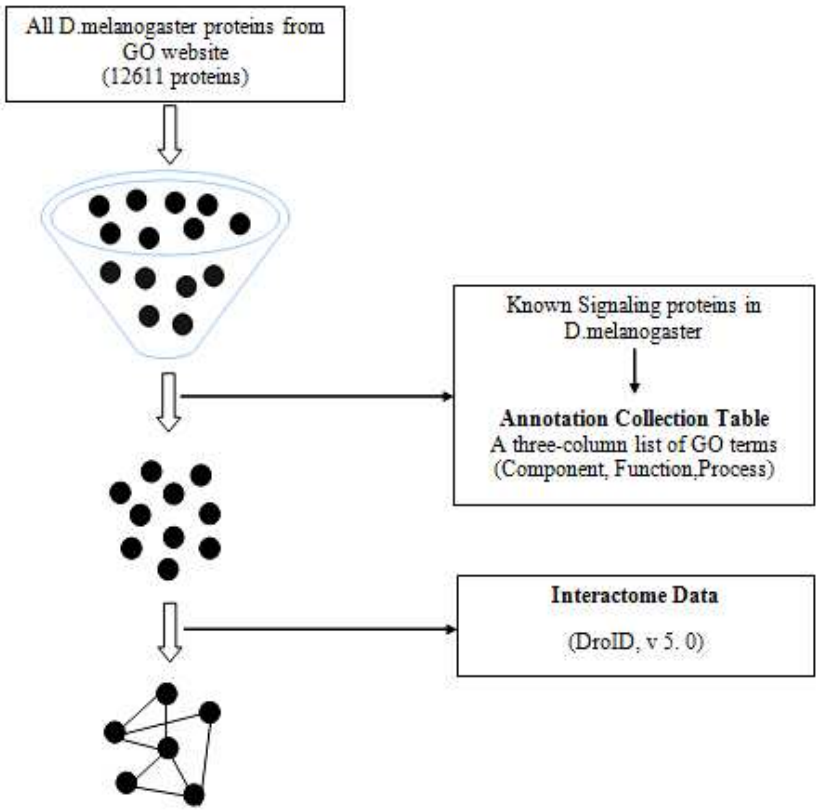


Figure 3.1. The schematic representation of the algorithm used for network reconstruction

3.3.2. Sequence Similarity Analysis

Sequence analysis is powerful means to obtain knowledge on protein regulation and function. This method is widely used to understand the evolutionary history of proteins (Horabin, 2007). Therefore, by using blastp algorithm (Altschul *et al*., 1997), the core protein's similarity and conservation among different species were investigated for both Wnt and Hedgehog signaling networks. Standard protein-protein BLAST (blastp) is used for finding similar sequences in protein databases. Blastp algorithm is freely available at http://blast.ncbi.nlm.nih.gov/Blast.cgi. Like other BLAST programs, blastp is designed to measure local similarity by using a matrix of similarity scores for all possible pairs of residues (Altschul *et al*., 1990).

In the present work, by using amino acid sequences of the core proteins for both Wnt and Hedgehog signaling pathway in *D. melanogaster* as initial query set, similarity and conservation among *C. elegans*, *H. sapiens*, *M. musculus*, *X. leavis* and *D.rerio* were searched.

3.3.3. Graph Theoretical Analysis

Graph theoretical analysis, in which proteins are called as nodes and interactions between these nodes as edges, provides an insight into the organization and structure of complex networks via introducing topological properties. The Cytoscape plugin NetworkAnalyzer (Assenov *et al*., 2008) computes and displays a large number of topological network parameters for directed and undirected networks loaded into Cytoscape. These parameters are the distribution of node degrees, the number of hubs (highly connected nodes), the mean path length, shortest path length and the network diameter (Assenov *et al*., 2008; Barabási and Oltvai, 2004). The input to the calculation is the list of binary interacting proteins. Observing the degree distribution of the proteins allows one to detect highly connected proteins which participate in significant numbers of interactions and play critical roles in the organization of the cellular protein interaction network.

Degree (Connectivity): Degree, k, is the most fundamental characteristic of a node and it indicates the number of edges the node has to other nodes.

Degree distribution: The probability of a selected node to have exactly k links is called as degree distribution, P(k). P(k) is computed by counting the number of nodes N(k) with k=1.2…edges and dividing by the total number of nodes N.

Shortest path and mean path length: The path length is the number of edges that should be passed through to travel between two nodes. While the shortest path is the path with the smallest number of edges between any two nodes, the mean path length, $< l >$, is the average of the all shortest paths between all nodes in a network.

Network diameter: The maximum length of shortest paths between two nodes is defined as network diameter, d.

In the past, complex networks were modeled as random networks. In random networks, P (k) follows a Poisson distribution ($P(k) < e^{-k}$), which indicates that most nodes have roughly the same number of edges, approximately equal to the network's mean

degree. On the contrary, many social and technological networks cannot be represented by random networks. These systems are described by scale-free networks, in which P(k) follows a power-law, $P(k) \approx k^{-\gamma}$, where γ is the degree exponent. In scale-free networks, a few highly connected nodes (hubs) are dominant and the rest of the less connected nodes are linked to the network via these hubs. In Figure 3.2, the comparison of random and scale-free networks is illustrated (Barabási and Oltvai, 2004, Jeong *et al*., 2000). Networks such as metabolic networks and protein-protein interaction networks generally approach a scale-free topology (Bader and Hogue, 2003).

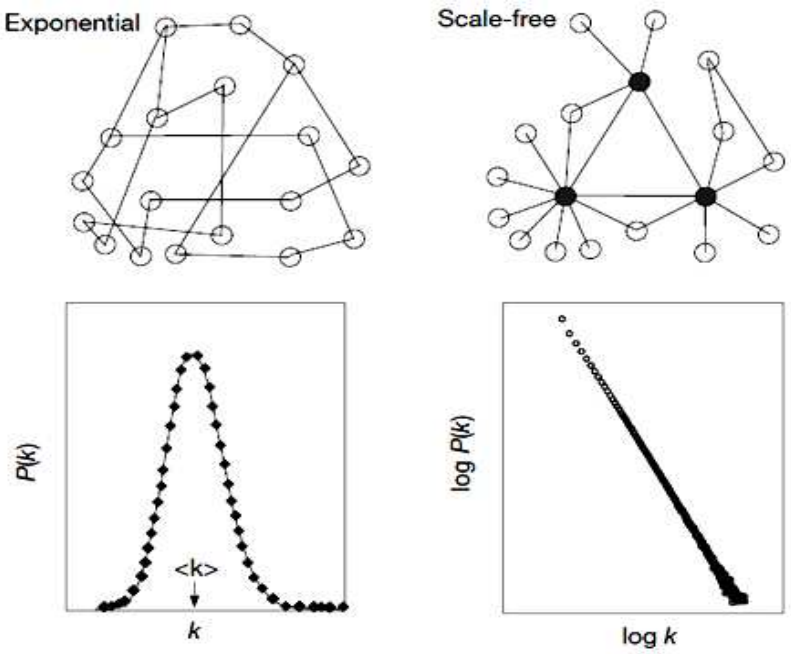


Figure 3.2. Representative structures of networks and their distributions (Jeong *et al*., 2000)

3.3.4. Network Decomposition Analysis

Network decomposition analysis enables us to decompose a protein interaction network into linear paths from inputs (i.e. ligands) to outputs (i.e. transcription factors). The linear paths of the reconstructed network were obtained by the NetSearch program (Steffen *et al*., 2002). NetSearch draws all possible linear paths of a specified length through the interaction list starting from an input protein and ending at an output protein. NetSearch algorithm, operating in MS-DOS screen, requires input files in the form of text files and these inputs are the separate files including the list of all proteins, binary

interactions between them, the ligand and the transcription factor. After supplying these inputs, NetSearch gives all linear paths starting with the ligand and ending with the transcription factor on the condition that the maximum path length between the ligand and the transcription factor is constrained by the user (see Appendix H.1 for the NetSearch script).

The participation frequencies of the proteins in the linear paths show their importance in the signal transduction. Therefore, the participation percentages of each protein were calculated for the reconstructed pathways to get an insight on the contributions of the proteins in the signal transduction from ligands to transcription factors (see Appendix H.2 for the script written in Excel for this calculation).

3.3.5. Module Detection and Analysis

Scale-free networks are known to have clustered regions and in biological networks these clustered regions correspond to molecular complexes defined as modules. MCODE (Bader and Hogue, 2003) is designed to find these highly interconnected or dense regions in a protein-protein interaction network. Detecting modules from protein interaction data is important, since it enables better understanding of the cellular role of the networks (Bader and Hogue, 2003).

Molecular Complex Detection (MCODE) algorithm (see Appendix H.3) detects locally dense regions in protein interaction networks in three stages, vertex (node) weighting, complex prediction and post-processing (to filter proteins from predicted complex). The algorithm first weights nodes based on their local network density. In the second stage, MCODE takes the node having the highest density as seed and moves outward from the seed including the nodes above a given threshold. At the final step, the proteins with a degree lower than 2 are filtered (Bader and Hogue, 2003).

After finding the modules in the Wnt and Hedgehog signaling networks, it was determined which Gene Ontology (GO) function is statistically overrepresented in the module of the networks via BiNGO (Maere *et al*., 2005). The Biological Networks Gene Ontology tool (BiNGO) provides two statistical tests for defining the overrepresentation in

a set of genes; the hypergeometric and binomial tests. The basic question answered by these tests is as follows: when sampling *X* genes (test set, the detected modules in our case) out of *N* genes (reference set, all proteins with GO annotations), what is the probability that *x* or more of these genes belong to a certain GO category shared by *n* of the *N* genes in the reference set? The hypergeometric test, answers this question in the form of a *P*-value (Maere *et al*., 2005). In this study, the hypergeometric test was used; the running parameters of BİNGO were given in Appendix H.4. The most recent annotation file can be downloaded from the GO website to BiNGO. The output of BiNGO is the most significant GO annotations with the lowest *P*-value.

3.3.6. Crosstalk Analysis

Signaling networks do not behave in isolation; on the contrary they interact with each other and form complex signaling networks. Therefore, to design therapeutic agents against the diseases caused by defects in signaling pathways, understanding the crosstalk between them is essential (Zielinski *et al*., 2009).

In this study, sharing of identical signaling molecules in different signaling pathways was used as an evidence of crosstalk. Moreover, a new measurement of crosstalk, network crosstalk, was also utilized. The difference in the degree of the node in the combined network including all considered pathways and the maximum degree of this node in any individual pathway represents the network crosstalk (see Appendix H.5 and Figure H.1). When the network crosstalk of a node gets a high value, it signifies that this node is a branching one connecting considered pathways (Zielinski *et al*., 2009).

4. RESULTS AND DISCUSSION

In the present study, the protein-protein interaction networks of canonical wnt and hedgehog signaling were reconstructed in *D. melanogaster* and the structural analysis of the networks was performed. The main drawback encountered during the reconstruction of a protein interaction network is that high-throughput methods for identifying protein interactions contain false positives (interactions that are identified by in vitro experiments but never take place in the cell) and false negatives (interactions that cannot be detected in the experiment but take place in the cell). Therefore, in order to improve the quality of data, diverse approaches have been tried by integrating genomic features such as Gene Ontology (GO) annotations and gene expression data (Arga *et al.* 2007, Lu *et al*. 2005; Patil and Nakamura, 2005; Liu and Zhao, 2004; Steffen *et al.* 2002).

4.1. Wnt/β-catenin Signaling

First, the known signaling proteins (core proteins) belonging to Wnt/β-catenin pathway was identified in *D. melanogaster*, and then, the conservation of these core proteins among different species was investigated. Next, the reconstruction process was carried out using GO annotations and interactome data. Finally, the structural analyses of the network were performed.

4.1.1. Known Wnt/β-catenin Signaling Proteins

34 proteins related to the Wnt/β-catenin signaling in *D. melanogaster* (Table 4.1) were identified through literature information (DasGupta *et al*. 2005a; KEGG PATHWAY Database; Latres *et al*. 1999; Liu *et al*. 2001; Boonen *et al*. 2009; Lauscher *et al*. 2007; Hirota *et al*. 2008; Ishitani *et al*., 1999; Gehrke *et al*. 2009).

The *Drosophila* proteins that participate in the canonical wnt signaling are shown in the pathway image, Figure 4.1. In addition to those displayed in Figure 4.1, the proteins lin19, skpC, sina, Psn, pont, Tak1, nmo, shf, Smox and Med were also included to the

canonical wnt signaling network referring to KEGG PATHWAY database. Below, the functions of the Wnt/β-catenin signaling core proteins are mentioned briefly.

Table 4.1. Core proteins of Wnt/β-catenin signaling pathway in *D. melanogaster*

General Name	**D. Melanogaster**		**General Name**	**D. Melanogaster**	
	Protein symbol	FlyBase ID		Protein symbol	FlyBase ID
Wnt	wg	FBgn0004009	Casein kinase I	CkIalpha	FBgn0015024
Dally	dally	FBgn0011577	β-catenin	arm	FBgn0000117
Dlp	**dlp**	**FBgn0041604**	Legless	lgs	FBgn0039907
Porcupine	**por**	**FBgn0004957**	Pygopus	pygo	FBgn0043900
Frizzled	fz	FBgn0001085	TCF	pan	FBgn0085432
	fz2	FBgn0016797	Groucho	gro	FBgn0001139
	fz3	FBgn0027343	CBP	nej	FBgn0015624
	fz4	**FBgn0027342**	Cul1	lin19	FBgn0015509
G alpha 0	G-oalpha47A	FBgn0001122	Skp1	skpC	FBgn0026175
LRP	arr	FBgn0000119	Siah-1	sina	FBgn0003410
Dishevelled	dsh	FBgn0000499	PS-1	Psn	FBgn0019947
Naked Cuticle	nkd	FBgn0002945	Protein 52	pont	FBgn0040078
APC	Apc	FBgn0015589	TAK1	Tak1	FBgn0026323
	Apc2	FBgn0026598	NLK	nmo	FBgn0011817
Axin	Axn	FBgn0026597	WIF-1	**shf**	**FBgn0003390**
GSK3	sgg	FBgn0003371	Smad4	Med	FBgn0011655
β-TrCP	slmb	FBgn0023423	Smad2	Smox	FBgn0025800

Wingless (wg): In *Drosophila* there are 7 Wnt genes, but only wingless (*Drosophila* Wnt1 homolog) signals through the canonical Wnt signaling pathway (Cohen *et al*., 2002).

Fz, fz2, fz3, fz4: Among the four Drosophila Frizzled proteins, frizzled (fz) and frizzled 2 (fz2) are the best characterized proteins. Frizzled receptors are 7 transmembrane molecules with cysteine-rich domain (CRD). Wnt proteins bind directly to the CRD of fz receptors (Nusse, 2005).

Arrow: Wnt signaling requires a transmembrane molecule of the LRP class, identified as the gene arrow (arr) in *Drosophila* (Nusse, 2005).

Dally: It has been identified as the product of division abnormally delayed (dally), a glypican molecule, involved in Wnt signaling. The results of the experiments indicate that dally may act as a co-receptor for the wnt ligand in *Drosophila*, wingless (wg), and that dally together with Drosophila Frizzled 2 (fz2), modulates both short and long-range activities of Wnt signaling (Lin and Perrimon, 1999).

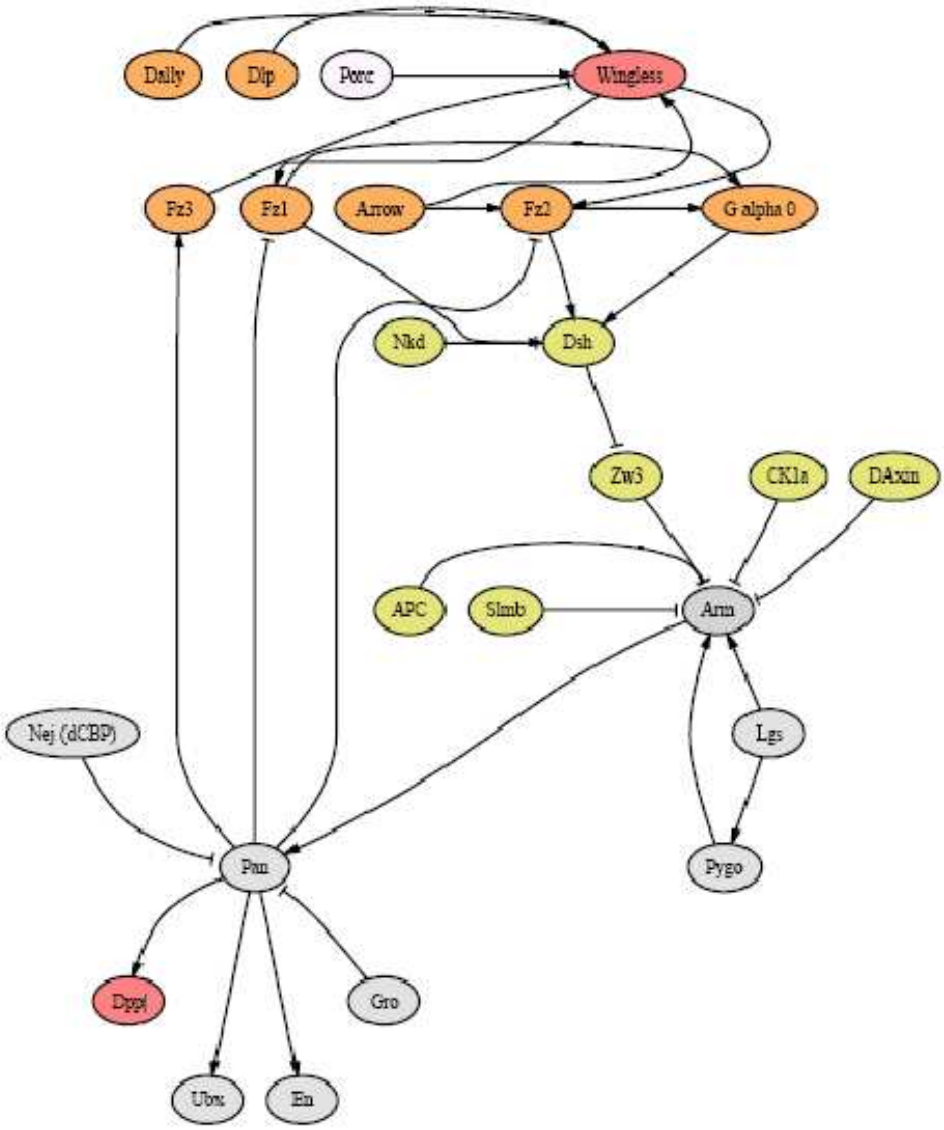


Figure 4.1. Canonical Wnt signaling pathway in *D. melanogaster* (DasGupta *et al*., 2005a)

Dally-like protein: The ectopic expression of Dally-like protein (dlp), a glypican molecule, in the wing disc inhibits Wnt signaling in *Drosophila* suggesting that dlp negatively regulates Wnt signaling in the wing disc (Han *et al*., 2005).

Porcupine: Wg requires porcupine (por) activity for its secretion. A number of data strongly support the model that por is specifically involved in Wnt signaling (Kadowaki *et al*., 1996).

Naked Cuticle: Naked Cuticle (nkd) antagonizes Wnt signaling, but potentially activates the planar cell polarity pathway. Nkd is a negative regulator of Wnt signaling and interacts with dsh through PDZ domain (McEwen and Peifer, 2001).

Legless and pygopus: Legless (lgs) and Pygopus (pygo) are co-activators of Wnt signaling in D*rosophila*; their roles in vertebrates are still incompletely understood (Klaus and Birchmeier, 2008). Lgs and pygo associate with β-catenin in the nucleus. Lgs binds directly to the N terminus of β-catenin and serves as an adaptor to attach pygo to the complex (Gordon and Nusse, 2006).

Groucho: In the non-activated state of Wnt signaling, cytoplasmic β-catenin levels remain low and TCF/LEF in the nucleus interacts with Grouchos (gro) to repress Wnt-specific target genes (Klaus and Birchmeier, 2008).

Pangolin: Pangolin (pan, also called dTcf) is a member of the TCF/LEF family of transcriptional regulators in *Drosophila* (DasGupta *et al*., 2005a).

Nej (dCBP): Nejire (nej) is a negative regulator of the Wnt pathway; it represses the transcription factor pan to antagonize Wnt signaling (Waltzer and Bienz, 1998).

Ubx, dpp, and en: Ultrabiothorax (ubx), decapentaplegic (dpp), and engrailed (en) are some of the pangolin-dependent Wnt target genes in *Drosophila* (DasGupta *et al*., 2005a).

Slmb, lin19 and skpC: Slimb (slmb), the *Drosophila* homolog of human F-box protein β-TrCP, forms a complex with lin19 (Cul1 in vertebrates) and skpC (Skp1 in vertebrates) and causes the proteosomol degradation of β-catenin when it is phosphorylated by the destruction complex (Latres *et al*., 1999).

G alpha0: Katanaev *et al*. (2005) provided evidence for the involvement of G proteins in the Wnt signal transduction pathway in flies. They demonstrated the role of G alpha0 subunit in transducing signals from frizzled receptors and provided evidence for the involvement of G proteins in both the canonical Wnt signaling and the planar cell polarity (PCP) pathway (DasGupta *et al*., 2005a).

Sina (Siah-1 in human): It has been found that Siah-1 interacts with the carboxyl terminus of APC and promotes degradation of β-catenin in mammalian cells. Degradation of β-catenin by Siah-1 was independent of GSKβ-mediated phosphorylation and did not require F box protein β-TrCP. These results indicate that APC and Siah-1 mediate a novel β-catenin degradation pathway (Liu *et al*., 2001).

Presenilin: Presenilin (psn) directly binds to β-catenin, and inhibits CRT (β-catenin-T cell factor-regulated transcription), which plays an essential role in the Wnt signaling pathway (Murayama *et al*., 1998).

Pontin: Pontin (pont), also known as RuvBL1, was identified as a TATA box–interacting protein (TIP). By directly binding to β-catenin, pontin enhances the transcriptional activity of the TCF/LEF/β-catenin transcription complex and thus the transcription of Wnt target genes (Lauscher *et al*., 2007).

Tak1 and nmo: Tak1 activation stimulates NLK (nmo in *Drosophila*) activity and downregulates transcriptional activation mediated by β-catenin and TCF. NLK phosphorylates TCF/LEF transcription factors and inhibits the interaction of the β-catenin-TCF complex with DNA (Ishitani *et al*., 1999).

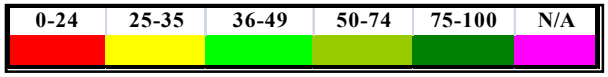
Shf (WIF-1 in human): WIF1, the negative regulator of Wnt signaling pathway, directly binds to Wnt ligands, therefore preventing them from binding to their receptors. (Gehrke *et al*., 2009).

Med (Smad4 in human), Smox (Smad2 in human): β-catenin/TCF transcriptional activity is enhanced by activated Smad2 and negatively regulated by the presence of Smad4 (Hirota *et al*. 2008).

4.1.2. Conservation of *D. melanogaster* Wnt/β-catenin Signaling Pathway Proteins

Before the reconstruction process, the conservation of the Wnt/β-catenin signaling core proteins in *D.melanogaster* was investigated among different species by sequence similarity analysis. Homologs of *D.melanogaster* Wnt/β-catenin signaling proteins were searched among the species C. *elegans* (CAEEL), *H. sapiens* (HUMAN), *M. musculus* (MOUSE), *X. leavis* (XENLA) and *D.rerio* (DANRE). Among the results, proteins with the best (lowest) Expect values were selected. The analyses were carried out at protein sequence level. High conservation rates of protein sequences support the idea that they function similarly.

The inputs of sequence similarity analysis are the amino acid sequences of the core proteins of canonical wnt signaling in *D. melanogaster*. The sequence information was retrieved from UniProt. The output of the analysis is the percentage of identical and conserved amino acids in 5 different organisms. A detailed table that represents the results of the sequence similarity analysis for canonical wnt signaling pathway is displayed in Appendix A (Table A.1). When the results are investigated, it is observed that *C. elegans*' proteins have the lowest similarity values. 15 of the 34 canonical wnt signaling core proteins have an identity lower than 36 per cent in *C. elegans*. However, the proteins in *H.sapiens* and *M. musculus* have high identity percentages. The identities of the proteins in *H. sapiens* are mostly above 50 per cent (20 out of 34 proteins). This finding verifies that *D. melanogaster* could be a superior model organism for cancer research. However, the homologs of the *Drosophila* proteins, dally, por, fz3, fz4, Axin1, lgs and shf in *H.sapiens* have low identities, lower than 36 per cent (see Figure 4.2). The proteins fz3 and fz4 in *Drosophila* are not well characterized when compared with fz and fz2, so this might be the reason for the low similarity value (Harris and Beckendorf, 2007). The sequence of the protein dally shows 28% identity and 44% similarity to the human Glypican protein which is in agreement with literature (Nakato *et al*., 1995). Furthermore, the protein shf also shows low similarity to the human ortholog WIF-1 protein. Both WIF-1 and shf have N-terminal signal sequences, followed by a single WIF domain and five EGF-like domains. Unlike WIF-1, shf contains two low-complexity domains between the signal sequence and the WIF domain, and a linker sequence between the WIF and EGF domains (Glise *et al*., 2005). So, the low similarity percentage between shf and WIF-1 may result from this fact.



	Protein	wg	dally	dlp	por	fz	fz2	fz3	fz4	G-oalpha47A	arrow	dsh	nkd	Apc	Apc2	Axn	sgg	slmb
		id%	id%	id%	id%	id%	id%	id%	id%	id%	id%	id %	id %	id%	id%	id%	id%	id%
DROME	Protein	wg	dally	dlp	por	FRIZ	fz-2	fz3	fz4	G-oalpha47A	arr	dsh	nkd	Apc	Apc2	Axn	sgg	slmb
CAEEL	Protein	WNT1	gpn-1	gpn-1	mom-1	mom-5	cfz-2	lin-17	mom-5	goa-1	lrp-1	mig-5	NCSl	apr-1	apr-1	pry-1	gsk-3	lin-23
HUMAN	Protein	WNT1	GPC5	GPC4	PORCN	FZD1	FZD5	FZD10	FZD4	GNAO1	LRP6	DVL-3	NKD1	APC	APC variant	AXIN1	GSK3B	BTRC
MOUSE	Protein	WNT1	GPC5	GPC6	Porcn	FZD7	FZD5	Fzd5	Fzd4	Gnao1	LRP6	DVL-3	NKD1	Apc	Apc	Axin1	Gsk3b	Btrc
XENLA	Protein	WNT1	gpc4	Xgly4	porcn	fzd1	fzd8	fzd5	fzd10-B	gna0	lrp5	DVL-3	NCS-1	apc	apc	axin1	gsk3b	TRCB
DANRE	Protein	WNT1	Zgc:171629	Zgc:171629	Zgc:55392	fzd7a	fzd8a	fzd10	fzd10	gnao1	lrp6	DIXC1	NKD1	apc	apc	axin1	gsk3b	fbxw11b

	Protein	arm	lgs	pygo	pan	gro	nej	lin19	CkIalpha	skpC	sina	Psn	pont	Tak1	nmo	shf	Med	smox
		id%	id%	id%	id%	id%	id%	%id	id%	%id	%id	%id	%id	%id	%id	%id	%id	%id
DROME	Protein	arm	lgs	pygo	pan	gro	nej	lin19	CkIalpha	skpC	sina	psn	pont	Tak1	nmo	shf	Med	smox
CAEEL	Protein	bar-1		C17G1.4a	pop-1	unc-37	cbp-1	cul-1	kin-19	skr-1	sia-1	sel-12	ruvb-2	mom-4	lit-1	apx-1	sma-4	sma-2
HUMAN	Protein	CTNNB1	BCL9	PYGO2	TCF7L2	TLE3	CREBBP	CUL1	CSNK1A1	SKP1	SIAH1	PSEN1	RUVBL1	MAP3K7	NLK	WIF1	SMAD4	SMAD2
MOUSE	Protein	Catenin beta-1	Bcl9	Pygo2	Tcf7l2	Tle4	Crebbp	Cul1	Csnk1a1	Skp1	Siah1b	Psen2	Ruvbl1	Map3k7	Nlk	Wif1	Smad4	Smad3
XENLA	Protein	beta-catenin	bcl9	Pygopus-2alpha	tcf7l1-A	tle4	LOC495689	MGC114992	csnk1a1	skp1	siah2	psen1	ruvbl1	map3k7	nlk.2	wif1	smad4	Mad2
DANRE	Protein	ctnnb1	bcl9l	pygo2	tcf7l1b	gro2	crebbpa	cul1b	csnk1a1	skp1	siah1	psen1	ruvbl1	map3k7	nlk2	wif1	Smad4	smad3a

Figure 4.2. Summary of sequence similarity analysis of the Wnt/β-catenin pathway

The canonical Wnt pathway is generally represented by its six key components including Wnt and Frizzled (the activators of the pathway), Dishevelled and GSK3 (the cytoplasmic transducers), and β-catenin and TCF/LEF (the nuclear factors). Sequence similarity analyses indicated that these six main components are conserved among the organisms ranging from *D.melanogaster* to *H.sapiens*. Within these proteins, WNT1 (the Human homolog of wg), FZD5 (the Human homolog of fz2), DVL-3 (the Human homolog of dsh), GSK3β (the Human homolog of sgg) and CTNNB1 (the Human homolog of arm) have identity percentages greater than 50 per cent. Furthermore, it should be noted that the homologs of *D.melanogaster* proteins share the same domains with the organisms C. *elegans*, *H. sapiens*, *M. musculus*, *X. leavis* and *D.rerio* which indicate the functional conservation (see Table A.1). All these results are in agreement with the literature information that canonical wnt signaling pathway components are evolutionary conserved.

4.1.3. Reconstruction of Wnt/β-catenin Signaling Network in *D. melanogaster*

After the identification of the known signaling proteins related to the Wnt/β-catenin pathway in *D. melanogaster*, the GO annotations of these core proteins form the annotation collection table (Appendix B, Tables B.1-3). 12611 *D. melanogaster* proteins obtained from the Gene Ontology website were tested by comparing their GO annotations with those of the core proteins. The proteins whose all three GO terms match with those in the annotation collection table were accepted to the network. Consequently, 1856 proteins passed this selection criterion. This procedure enabled one to choose the proteins having high probability to have function in the canonical wnt signal transduction. Next, the physical protein interactions of these 1856 proteins were found by using the DroID. 1168 of these proteins could not be included into the network as either the GO terms of their interacting partners do not overlap with those in the annotation collection table or they do not have interactome data.

Within these 688 proteins accepted to the network, 8 of the core proteins are absent since they have no interaction data or their interacting partners do not fulfill the selection criterion based on GO annotations. Also some essential direct interactions between core proteins are missing in the network such as the interaction between the ligand, wg, and the receptor, fz. To overcome this problem, some putative interactions in *H. Sapiens* are added

Table 4.2. Putative interactions in Wnt/β-catenin signaling network

Protein symbol		FlyBase ID	
Interactor A	**Interactor B**	**Interactor A**	**Interactor B**
wg	fz	FBgn0004009	FBgn0001085
wg	arr	FBgn0004009	FBgn0000119
wg	fz2	FBgn0004009	FBgn0016797
arr	fz2	FBgn0000119	FBgn0016797
sgg	arm	FBgn0003371	FBgn0000117
sgg	Apc	FBgn0003371	FBgn0015589
skpC	lin19	FBgn0026175	FBgn0015509
Psn	arm	FBgn0019947	FBgn0000117
CkIalpha	Apc	FBgn0015024	FBgn0015589
Axn	sgg	FBgn0026597	FBgn0003371
Axn	arm	FBgn0026597	FBgn0000117
Axn	Apc	FBgn0026597	FBgn0015589
Axn	dsh	FBgn0026597	FBgn0000499
Apc	arm	FBgn0015589	FBgn0000117
Apc	sina	FBgn0015589	FBgn0003410
nmo	pan	FBgn0011817	FBgn0085432
pont	arm	FBgn0040078	FBgn0000117
slmb	lin19	FBgn0023423	FBgn0015509
slmb	skpC	FBgn0023423	FBgn0026175
fz	dsh	FBgn0001085	FBgn0000499

to the network by homology search using BLAST. In this approach, first the homolog of the protein with the missing interaction is found in *H. Sapiens*, and then the protein-protein interactions of the homolog protein are obtained. If the interacting proteins passed the selection criterion, their homologs in *D. melanogaster* are accepted as candidate interacting proteins. By this approach, 19 new putative interactions are added to the network (Table 4.2). Moreover, by homology search, 5 known wnt signaling proteins that could not be included to the netwok due to their missing interactions were added which are wg, arr, skpC, Psn and CKIalpha. All of these core proteins are essential for the Wnt/β-catenin signaling. It was reported that canonical wnt signaling is only mediated when both Fz and LRP (arr in *Drosophila*) are complexed with Wnt (wg in *Drosophila*) (Giles *et al*., 2003). The other essential protein CKIalpha is a member of the destruction complex and needed for β-catenin phosphorylation. Furthermore, β-Trcp (human homolog of *Drosophila* Slimb) forms a complex with Cul1 (lin19 in *Drosophila*) and Skp1 (skpC in *Drosophila*) and mediates the degradation of β-catenin (Latres *et al*., 1999). Presenilin (Psn in *Drosphila*) which directly binds to β-catenin, and contributes to β-catenin degradation is also another essential protein for the wnt signaling. It plays an inhibitory role by preventing β-catenin-TCF-regulated transcription (Murayama *et al*., 1998; Boonen *et al*., 2009). In addition, the

interaction between fz and dsh proteins was included to the network as a consequence of literature search (Wong *et al*. 2003).

Eventually, an interaction network of 693 nodes and 1278 edges is obtained for the canonical wnt signaling. When the isolated smaller parts are removed the resulting protein-protein interaction network consists of 656 proteins and 1253 interactions among them (Appendix C, Table C.1) and an overview of the network is displayed in Figure 4.3. The core protein por is removed from the network since it forms an isolated part in the network. The 4 core proteins that are not included in the reconstructed network are given in bold in Table 4.1.

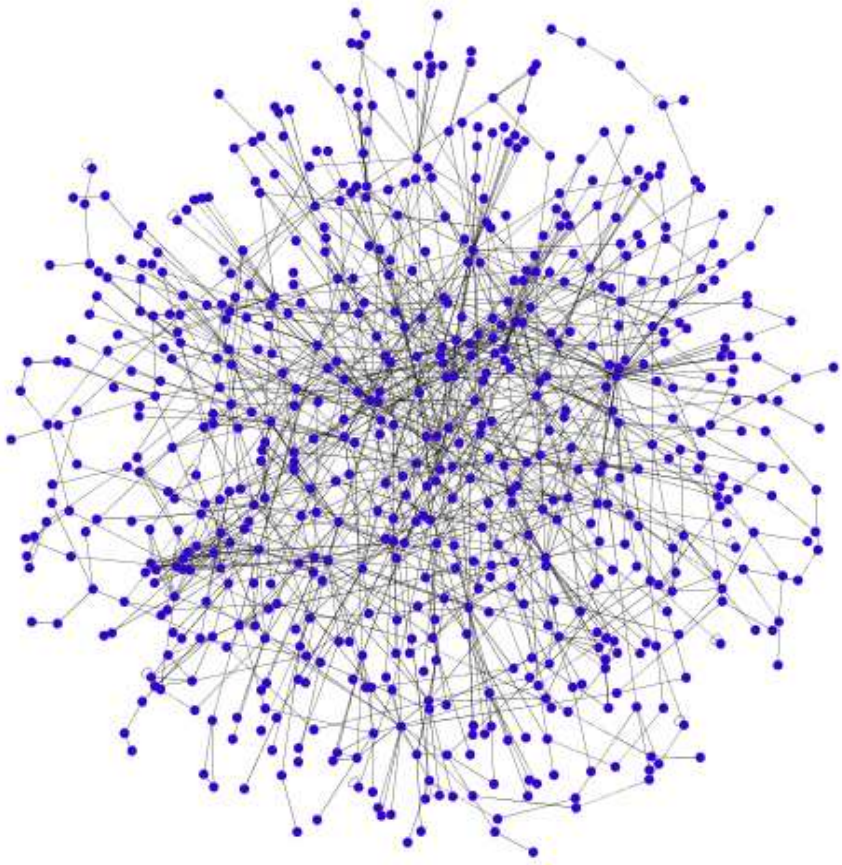


Figure 4.3. Representation of the reconstructed Wnt/β-catenin signaling network (produced by Cytoscape 2.6.3)

4.1.4. Graph Theoretic Analysis

The topological analysis of the reconstructed canonical wnt signaling network, with 656 nodes and 1253 edges, was performed using Network analyzer plugin (ver. 2.6.1) of

Cytoscape (ver. 2.6.3). The network diameter and the mean path length were found as 13 and 4.8, respectively, indicating the small-world topology. These calculated topological properties of the reconstructed network are in agreement with literature (see Table 4.3). Several protein interaction networks similarly have small-world character. The degree distribution of the reconstructed wnt network approximates a power law model ($P(k) \approx k^{-\gamma}$, γ=1.78, R^2=0.93) revealing a scale-free network with a few nodes having high degree and the rest having low degree (Figure 4.4). Having small-world features with scale-free topology is a general characteristic of complex biological networks (Maslov and Sneppen, 2002; Jeong *et al*. 2001; Wagner and Fell, 2001; Jeong *et al*. 2000).

Table 4.3. Graph theoretic properties of the protein interaction networks

Model	**Number of nodes**	**Number of interactions**	**Mean Path Length**	**Diameter**	**Reference**
Wnt/β-catenin (D.melanogaster)	656	1253	4.80	13	Present work
Hedgehog (D.melanogaster)	568	975	4.80	14	Present work
EGFR	329	1795	4.70	11	Tekir *et al*., 2009
S. cerevisiae (signaling)	1363	3649	6.81	9	Arga *et al*., 2007
DIP (S. cerevisiae-Core)	2640	6600	5.00	13	Wu *et al.,* 2005
Ito (S. cerevisiae-Core)	797	1560	6.2	16	Yook *et al*., 2004
DIP (D. melanogaster)	7451	22819	4.40	11	Wu *et al*., 2005
DIP (C. elegans)	2638	4030	4.80	14	Wu *et al*., 2005
DIP (H. pylori)	710	1420	4.10	9	Wu *et al*., 2005
DIP (H. sapiens)	1065	1369	6.80	21	Wu *et al*., 2005
DIP (E. coli)	553	761	5.50	16	Wu *et al*., 2005
DIP (M. musculus)	329	286	3.60	9	Wu *et al*., 2005

The connectivity values of all proteins in the reconstructed Wnt/β-catenin signaling network are given in Appendix D. The hubs of the reconstructed Wnt/β-catenin signaling network were determined as ci, Mer and ptc having the highest connectivity values of 38, 36 and 27, respectively (see Table D.1). Cubitus interruptus (ci) and patched (ptc) proteins are actually key components of the Hedgehog signaling pathway; however, they also participate in the Wnt signaling pathway. Ci interacts with the core proteins of the Wnt signaling pathway. These interacting core proteins are the transmembrane frizzled receptor

(fz3) and the protein nejire (nej). Furthermore, the protein ptc interacts with the transmembrane receptor fz2 and sina that interacts with APC and promotes degradation of β-catenin (Liu *et al*., 2001). Merlin (Mer) functions as a negative growth regulator or tumor suppressor. There is experimental evidence that merlin has the biological process terms such as cell-cell signaling and regulation of signal transduction. Besides, it has been reported that overexpression of merlin reduces the canonical wnt activity by decreasing Fz1 expression or increasing DKK expression (Lau *et al*., 2008; Bosco *et al*., 2010).

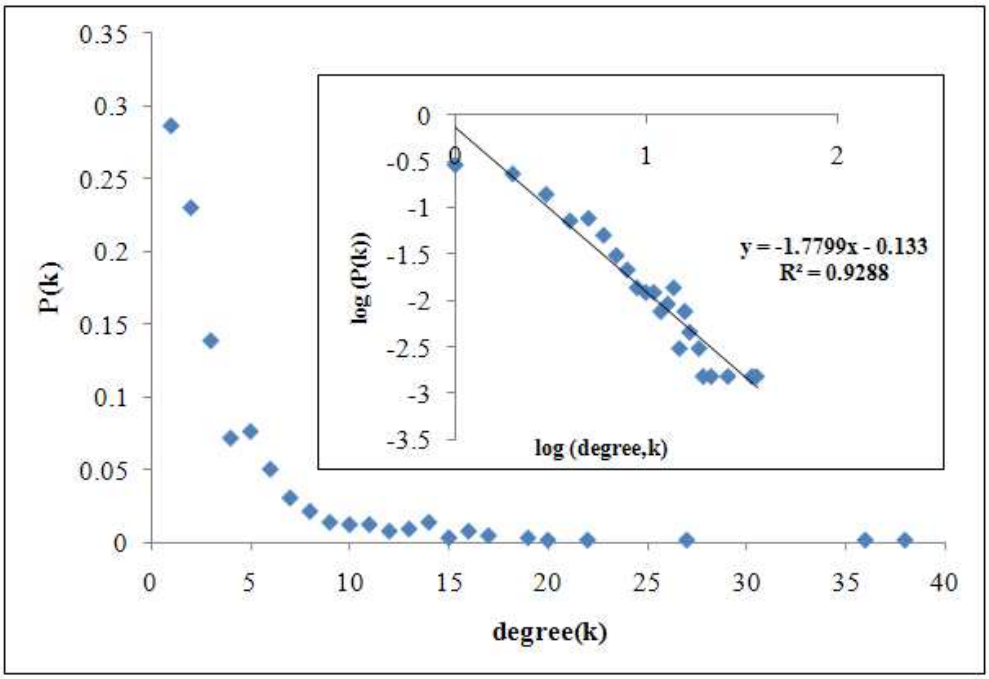


Figure 4.4. Degree distribution of the canonical Wnt signaling network

4.1.5. Network Decomposition Analysis

The linear paths in the reconstructed Wnt/β-catenin network were detected using NetSearch algorithm of Steffen *et al*. (2002). Wingless (wg, canonical wnt ligand in *Drosophila*) and pangolin (pan, transcription factor of canonical wnt pathway in *Drosophila*) proteins were used as the input and the output of the signaling network, respectively.

The shortest path length between wg and pan was found as 5 as the shortest 7 linear paths include 6 proteins connected linearly by 5 interactions (see Table E.1). Higher path

lengths were also tried in order to cover all the proteins in the network but due to the insufficient server capacity (computational power), a maximum number of 11 steps could be achieved (Table 4.4). There are 238753 linear paths starting from wg leading to the transcription factor pan at the maximum 11 steps. 397 of 656 proteins (61%) and 21 of 30 core proteins (70%) in the reconstructed network exist in these paths. 41486 linear paths within these 238753 paths include the key mediator of canonical wnt signaling, arm (*Drosophila* homolog of β-catenin).

Table 4.4. The network decomposition analysis in Wnt signaling network

Number of steps	**Number of linear paths**	**Number of core proteins exist in the paths**	**Number of nodes exist in the paths**
5	7	9 (30%)	17 (3%)
6	48	15 (50%)	55 (8%)
7	282	17 (57%)	104 (16%)
8	1449	18 (60%)	199 (30%)
9	8381	20 (67%)	289 (44%)
10	44954	21 (70%)	361 (55%)
11	238753	21 (70%)	397 (61%)

The percentages of each protein contributing to 41486 linear paths (373 proteins) were also found (see Table F.1). The proteins wg, pan and arm are included in all the linear paths (100 % participation) since they are the input, output and key proteins, respectively. The proteins having a participation percentage over 20% in these linear paths following the wg, pan and arm are also listed in Table 4.5. These proteins were found to be involved in linear paths with the highest participation values since they either bind to the input and output proteins or to the core proteins which are central to many paths in the network. The 5 proteins out of these 7 proteins which are frizzled receptors (fz and fz2), nejire (nej) which represses pan to antagonize Wnt signaling, ultrabiothorax (ubx) which is the pan dependent Wnt target gene, and disheveled (dsh) which in its active state prevents the destruction complex to phosphorylate β-catenin (arm in *Drosophila*) are already the known important proteins related to the canonical wnt signaling. Another protein, ttk has also direct interaction with the dsh protein that is central to many paths in the reconstructed network. The proteins fru, HLH3B, Rpt4, csw, vvl, CLIP-190, Cdk8, plexA, gbb, dos, acj6, loqs, CG1894 and jar participated in only one linear path within the Wnt network which means that the absence of these proteins does not affect the signaling mechanism.

Table 4.5. Proteins with the highest percentages in the Wnt linear paths

Protein	Percentage in linear paths (%)	Connectivity values
fz2 (frizzled2)	67,94	5
ptc (patched)	54,42	27
dsh (disheveled)	36,92	12
nej (nejire)	34,77	9
fz (frizzled)	32,10	4
ubx (ultrabiothorax)	30,10	14
ttk (tramtrack)	21,20	17

4.1.6. Module Detection and Analysis

Recent studies suggest that protein-protein interaction networks are composed of modules which are groups of proteins performing a certain biological function together. Therefore, detecting modules in biological networks enables better understanding of the cellular role of these networks (Bader and Hogue, 2003; Przulj *et al*., 2004). On this basis, MCODE was used to detect possible modules in the reconstructed Wnt network. Of the 656 proteins, 83 were clustered into 12 modules (Table 4.6).

The biological significance of the molecular functions of these modules was also tested by utilizing BİNGO. Significantly over-represented molecular function terms which are furthest down the GO hierarchy for each module are listed in Table 4.7. Many of the proteins in the modules correspond to binding proteins, cellular enzymes and transcriptional regulatory proteins. Therefore, over-represented biological functions that these modules share are under the main categories of the related GO annotation tree; binding, catalytic activity and transcriptional activity.

Table 4.6. Modules detected in the reconstructed Wnt network

Module	Score	Nodes	Edges	Node IDs
1	3,4	9	38	E(spl), da, HLHm7, HLHm5, gro, HLHm3, HLHmdelta, HLHmbeta, HLHmgamma
2	2,5	6	15	e(y)3, Snr1, Act5C, brm, pont, osa
3	2,3	6	14	Rbf, E2f2, mip130, Rbf2, Myb, Dp
4	2,0	5	13	E(z), Rpd3, Pcl, esc, Su(z)12
5	1,8	5	10	Rpt1, Pros45, Rpt4R, Rpt4, Pros26.4
6	1,6	12	24	arm, ebi, CtBP, wek, dl, tamo, phyl, ttk, sina, Apc, Axn, sgg
7	1,5	4	6	e(y)1, Ada2b, Rpb4, Spt3
8	1,5	4	6	aPKC, numb, par-6, baz
9	1,2	5	7	su(Hw), Trl, Cp190, smt3, mod(mdg4)
10	1,2	13	15	CHIP, Hsc70-4, ago, e(r), dx, MED6, MED20, MED17, Dl, CG34422, N, chinmo, cos
11	1,0	6	8	spn-A, tou, lig3, Mical, apt, bip2
12	1,0	3	3	Bgb, run, Bro

Table 4.7. Most significant molecular functions of modules in the Wnt network

Module id	GO-ID	P-value	Description
1	43565	3,93E-13	sequence-specific DNA binding
2	16251	1,06E-03	general RNA polymerase II transcription factor activity
3	3677	3,49E-07	DNA binding
4	46976	4,55E-04	histone lysine N-methyltransferase activity (H3-K27 specific)
5	16887	2,96E-08	ATPase activity
6	8013	1,64E-05	beta-catenin binding
7	4404	6,55E-06	histone acetyltransferase activity
8	5080	1,09E-03	protein kinase C binding
9	8195	4,09E-03	phosphatidate phosphatase activity
10	5515	2,56E-06	protein binding
11	3677	6,51E-04	DNA binding
12	3713	9,43E-06	transcription coactivator activity

4.2. Hedgehog Signaling

The reconstruction of the Hedgehog signaling network was also performed in *D. melanogaster*. As it was done for the Wnt signaling proteins, the conservation of the core proteins of Hedgehog signaling pathway in *D. melanogaster* was investigated among different species prior to the reconstruction process. The structural analyses of the reconstructed network which are graph theoretic analysis, network decomposition analysis and module detection were performed after the completion of the reconstruction step.

4.2.1. Known Hedgehog Signaling Proteins

23 proteins related to the Hedgehog signaling in *D. melanogaster* (Table 4.8) were identified as a result of literature information (Jacob and Lum, 2007; KEGG PATHWAY Database; Wang and Price, 2008).

Table 4.8. Core proteins of Hedgehog signaling pathway in *D. melanogaster*

Protein symbol	**FlyBase ID**	**Protein symbol**	**FlyBase ID**
ttv	**FBgn0020245**	smo	FBgn0003444
disp	**FBgn0029088**	cos	FBgn0000352
rasp (ski)	**FBgn0024194**	fu	FBgn0001079
dally	FBgn0011577	Pka-C1	FBgn0000273
dlp	**FBgn0041604**	CkIα	FBgn0015024
Rfabg (Lipophorin)	FBgn0087002	sgg	FBgn0003371
iHog	FBgn0031872	Su(fu)	FBgn0005355
shf	**FBgn0003390**	slmb	FBgn0023423
boi	FBgn0040388	Roc1a	FBgn0025638
hh	FBgn0004644	lin19	FBgn0015509
ptc	FBgn0003892	ci	FBgn0004859
Gprk2	**FBgn0004834**		

The *Drosophila* proteins that participate in the hedgehog signaling are shown in the pathway image, Figure 4.5. In addition to those displayed in Figure 4.5, the proteins lin19 and Roc1a were also included to the hedgehog signaling network (Wang and Price, 2008). The functions of the Hedgehog signaling core proteins are briefly mentioned below.

Tout-velu (ttv): Ttv is required for the production of heparan sulfate proteoglycans (HSPG) involved in Hh movement, such as dally and dlp. Ttv regulates synthesis of proteoglycans and functions to allow movement of hh (Han *et al*. 2004; Mullor *et al*., 2002).

Dally and dally-like (dlp): Dally and dlp, two *Drosophila* glypican members of the heparan sulphate proteoglycan (HSPG) family, are essential for hh transport through tissues (Han *et al*. 2004).

Lipophorins: Lipophorins are lipid-transporting particles that are important for Hedgehog movement. They can be found in a complex with hh and glypican family members. Interactions between lipophorins and the glypicans are mediated by the heparan sulfate moieties found on glypicans and these interactions are important for hh movement (Eugster *et al*., 2007).

iHog and boi: Transmembrane proteins iHog and boi have roles in facilitating the binding of hh to cells, also they increase the binding affinity of hh for the signaling receptor ptc (Varjosalo and Taipale, 2007).

Shifted: The shifted (shf) protein, whose known role is to bind to extracellular Wnts and inhibit their activity, is also required for the accumulation and movement of hh (Glise *et al*., 2005).

Gprk2: Drosophila Gprk2, a member of the G protein-coupled receptor kinases, plays a key role in the Smo signal transduction pathway. It is critically required to generate high levels of Hedgehog signaling in the wing disc (Molnar *et al*., 2007).

Supernumerary limb (slmb), Cullin 1 (lin19 in *Drosophila*), and Roc1a: Slmb, lin19 and Roc1a which are the components of an SCF E3 ubiquitin ligase, are needed for ci processing. Slmb binds directly to cubitus interruptus (ci) but only when ci has been phosphorylated on multiple sites by protein kinase A (Pka), glycogen synthase kinase 3 (GSK-3 or sgg), and casein kinase I (CkI), explaining the requirement of these kinases for ci processing (Wang and Price, 2008). In addition, Pka and CkIα phosphorylate smo at

several sites in the presence of hedgehog, it has been shown that smo phosphorylation by these kinases is essential for its activity and membrane accumulation (Molnar *et al*. 2007).

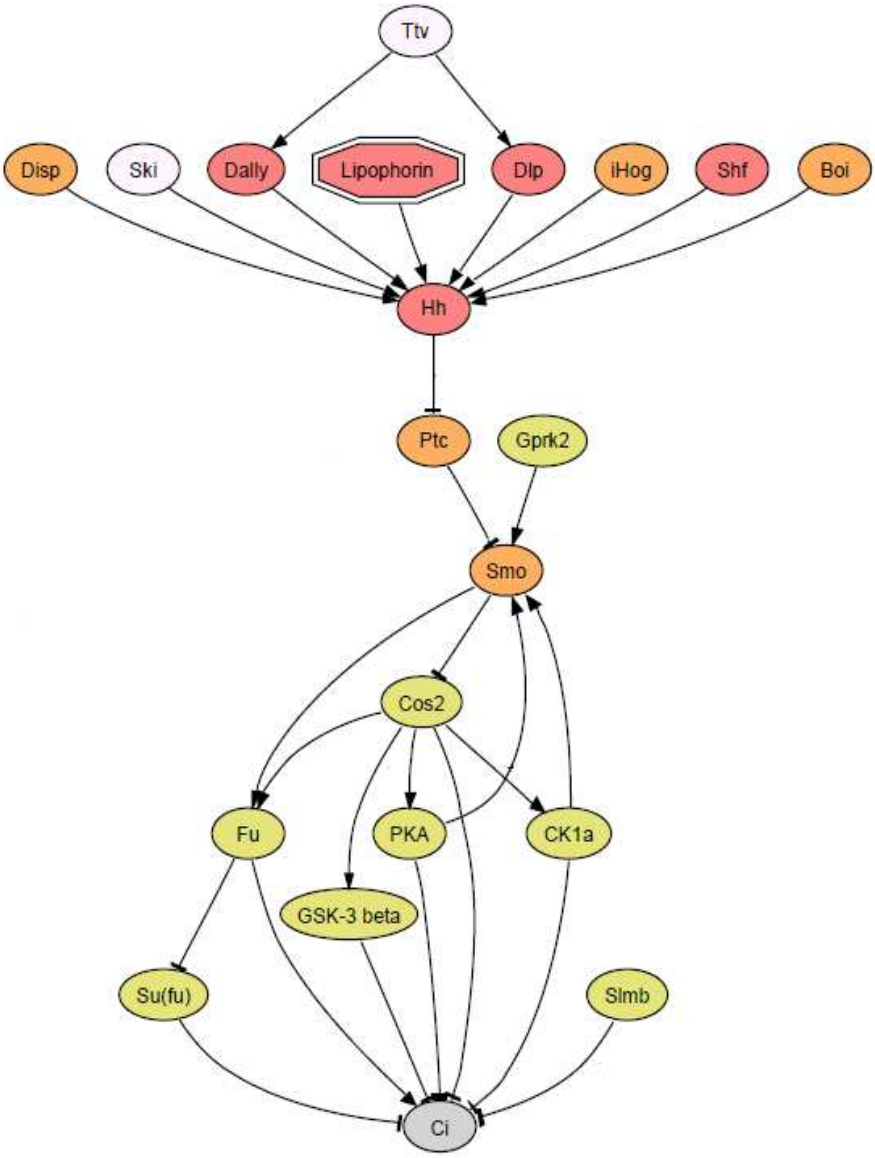


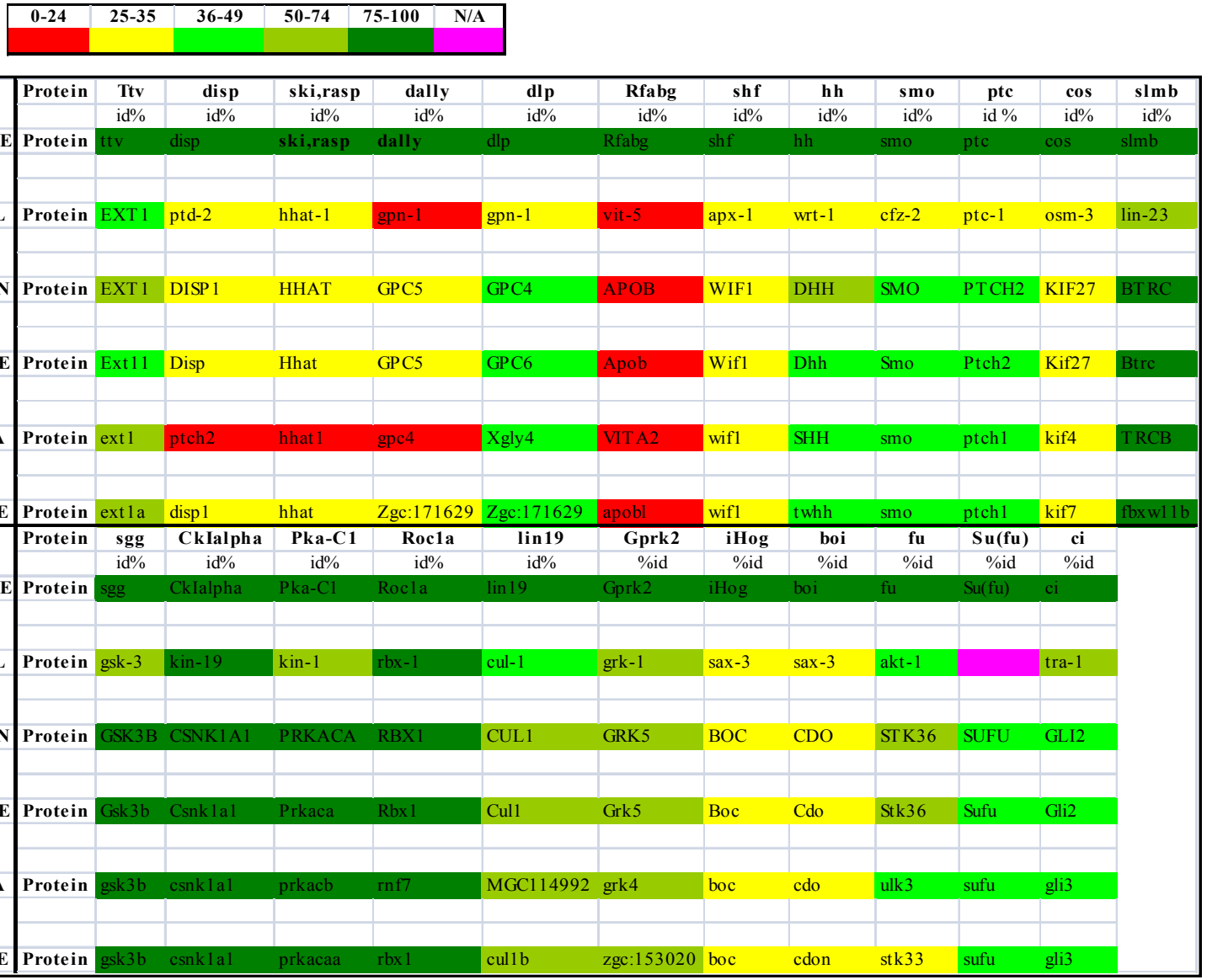
Figure 4.5. Hedgehog signaling pathway in *D. melanogaster* (Jacob and Lum, 2007)

4.2.2. Conservation of *D. melanogaster* Hedgehog Signaling Pathway Proteins

The conservation of the Hedgehog signaling core proteins in *D.melanogaster* was investigated among different species (*C. elegans*, *H. sapiens*, *M. musculus*, *X. leavis* and *D.rerio*) by sequence similarity analysis. High conservation rates of protein sequences support the idea that they function similarly. A detailed table that represents the results of

the sequence similarity analysis for the hedgehog signaling proteins is given in Appendix A (Table A.2). When the results are investigated, it is observed that *C. elegans*' proteins have the lowest similarity values. However, the amino acid identity percentages of the proteins in *H.sapiens*, *M. musculus*, *X. leavis* and *D.rerio* are higher and close to each other. Besides, the identity values of the hedgehog signaling proteins in *D.melanogaster* and *H. sapiens* are satisfactory except the protein Rfabg (Figure 4.6). This finding verifies that *D. melanogaster* could be a good model organism for experimental and in silico studies for Hedgehog signaling.

Despite the low amino acid identity (<36%), the molecules disp, iHog and boi (Boc and Cdo in vertebrates), and shf (WIF-1 in vertebrates) have their vertebrate counterparts which suggest that many of the steps up to the binding of hh to its receptor are conserved. The low sequence identity between *Drosophila* proteins, iHog and boi, and related vertebrate proteins, Cdo and Boc, may result from the different number of fibronectin type III (FNIII) and immunoglobulin (Ig) domains they contain (Yao *et al*., 2006). Furthermore, the components between the smo and the transcription factor, ci, are largely conserved; the human homologs of the *Drosophila* proteins slmb, sgg, CkIα and PkaC1, which have roles in processing ci, have identity percentages above 75 per cent (see Figure 4.6). Consequently, the results of the sequence similarity analysis are in agreement with the literature information that hedgehog signaling pathway components are evolutionary conserved. However, according to a body of work, some divergences in the Hedgehog signaling mechanism appear between *Drosophila* and vertebrates. For example, the mammalian homolog of *Drosophila* cos protein, Kif27, does not affect Hedgehog signaling. Conversely, Su(fu) plays the role of cos in mammals (Horabin, 2007; Varjosalo and Taipale, 2007).



	Protein	Ttv	disp	ski,rasp	dally	dlp	Rfabg	shf	hh	smo	ptc	cos	slmb
		id%	id%	id%	id%	id%	id%	id%	id%	id%	id %	id%	id%
DROME	Protein	ttv	disp	ski,rasp	dally	dlp	Rfabg	shf	hh	smo	ptc	cos	slmb
CAEEL	Protein	EXT1	ptd-2	hhat-1	gpn-1	gpn-1	vit-5	apx-1	wrt-1	cfz-2	ptc-1	osm-3	lin-23
HUMAN	Protein	EXT1	DISP1	HHAT	GPC5	GPC4	APOB	WIF1	DHH	SMO	PTCH2	KIF27	BTRC
MOUSE	Protein	Ext1l	Disp	Hhat	GPC5	GPC6	Apob	Wif1	Dhh	Smo	Ptch2	Kif27	Btrc
XENLA	Protein	ext1	ptch2	hhat1	gpc4	Xgly4	VITA2	wif1	SHH	smo	ptch1	kif4	TRCB
DANRE	Protein	ext1a	disp1	hhat	Zgc:171629	Zgc:171629	apobl	wif1	twhh	smo	ptch1	kif7	fbxw11b

	Protein	sgg	CkIalpha	Pka-C1	Roc1a	lin19	Gprk2	iHog	boi	fu	Su(fu)	ci
		id%	id%	id%	id%	id%	%id	%id	%id	%id	%id	%id
DROME	Protein	sgg	CkIalpha	Pka-C1	Roc1a	lin19	Gprk2	iHog	boi	fu	Su(fu)	ci
CAEEL	Protein	gsk-3	kin-19	kin-1	rbx-1	cul-1	grk-1	sax-3	sax-3	akt-1		tra-1
HUMAN	Protein	GSK3B	CSNK1A1	PRKACA	RBX1	CUL1	GRK5	BOC	CDO	STK36	SUFU	GLI2
MOUSE	Protein	Gsk3b	Csnk1a1	Prkaca	Rbx1	Cul1	Grk5	Boc	Cdo	Stk36	Sufu	Gli2
XENLA	Protein	gsk3b	csnk1a1	prkacb	rnf7	MGC114992	grk4	boc	cdo	ulk3	sufu	gli3
DANRE	Protein	gsk3b	csnk1a1	prkacaa	rbx1	cul1b	zgc:153020	boc	cdon	stk33	sufu	gli3

Figure 4.6. Summary of sequence similarity analysis of the Hedgehog pathway

4.2.3. Reconstruction of Hedgehog Signaling Network in *D. melanogaster*

The same method used in the reconstruction of Wnt signaling network was followed for the reconstruction of Hedgehog signaling network. After the identification of the Hedgehog signaling core proteins in *D.melanogaster*, the annotation collection table belonging to these core proteins was generated (Appendix B, Table B.4-7).

As it was done for the Wnt pathway, 12611 *D. melanogaster* proteins were tested by using the GO annotations of the 23 core proteins known to belong to the Hedgehog pathway. 1651 proteins passed this selection criterion. Next, the physical protein interactions of these 1651 proteins were found by using the DroID. Consequently, an interaction network of 565 nodes and 958 edges was obtained for Hedgehog signaling. Among these 565 proteins accepted to the network, 6 proteins of the cores cannot be included because of the missing interaction partners. Again, as it was the case for the Wnt pathway, some essential direct interactions between the core proteins are missing in the network such as the interaction between the ligand, Hh, and the receptor, ptc. To overcome this problem, some putative interactions were added to the network by homology search in *H. sapiens* using BLAST and literature search. In the homology search, first the homolog of the protein with the missing interaction is found in *H. sapiens*, and then the protein-protein interactions of the homolog protein are obtained. If the interacting proteins passed the selection criterion, their homologs in *D. melanogaster* are accepted as candidate interacting proteins. By homology search 7 putative interactions and by literature search 10 putative interactions are added to the network (Table 4.9). The core protein CkIα was added to network via homology search. It is an important protein for Hedgehog signaling since in the absence of hh, CkIα phosphorylate ci together with Pka-C1 and sgg leading to the proteolysis of ci to its repressor form. Furthermore, in the presence of hh, Pka and CkI phosphorylate smo which is essential for smo activity (Molnar *et al*. 2007).

Eventually, an interaction network of 568 nodes and 975 edges is obtained for Hedgehog signaling. When the isolated smaller parts are removed the resulting protein-protein interaction network consists of 523 proteins and 945 interactions among them (Appendix C, Table C.2) and an overview of the network is displayed in Figure 4.7. The core protein ttv is removed from the network, since it was isolated from the network. The 6

core proteins not included in the reconstructed hedgehog signaling network are given in bolds in Table 4.8.

Table 4.9. Putative interactions in Hedgehog signaling network

	FlyBase ID		**Protein symbol**		
	Interactor A	**Interactor B**	**Interactor A**	**Interactor B**	**References**
literature search	FBgn0004644	FBgn0003892	hh	ptc	Chen and Struhl, 1996
	FBgn0000352	FBgn0000273	cos	Pka-C1	Zhang *et al*., 2005
	FBgn0000352	FBgn0015024	cos	CkIalpha	Zhang *et al*., 2005
	FBgn0000352	FBgn0003371	cos	sgg	Zhang *et al*., 2005
	FBgn0023423	FBgn0004859	slmb	ci	Wang and Price, 2008
	FBgn0000273	FBgn0004859	Pka-C1	ci	Zhang *et al*., 2005; Wang and Price, 2008
	FBgn0015024	FBgn0004859	CkIalpha	ci	Zhang *et al*., 2005; Wang and Price,2008
	FBgn0003371	FBgn0004859	sgg	ci	Zhang *et al*., 2005; Wang and Price,2008
	FBgn0000273	FBgn0003444	Pka-C1	smo	Jia *et al*., 2004
	FBgn0015024	FBgn0003444	CkIalpha	smo	Jia *et al*., 2004
homology search	FBgn0040388	FBgn0031872	boi	iHog	
	FBgn0003892	FBgn0003444	ptc	smo	
	FBgn0023423	FBgn0015509	slmb	lin19	
	FBgn0003371	FBgn0000117	sgg	arm	
	FBgn0003371	FBgn0015589	sgg	Apc	
	FBgn0015024	FBgn0015589	CkIalpha	Apc	
	FBgn0023423	FBgn0026175	slmb	skpC	

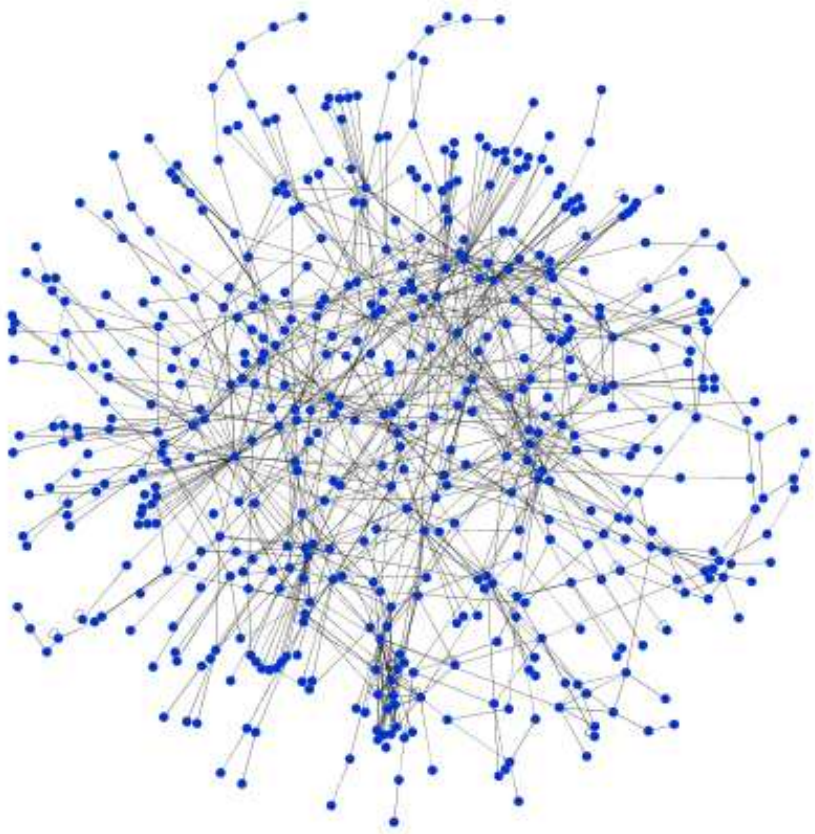


Figure 4.7. Representation of the reconstructed Hedgehog signaling network (produced by Cytoscape 2.6.3)

4.2.4. Graph Theoretic Analysis

The topological analysis of the reconstructed Hedgehog signaling network, with 568 nodes and 975 edges, was performed using Network analyzer plugin. The network diameter and the mean path length were found as 14 and 4.8, respectively. The reconstructed Hedgehog signaling network has small-world character like several protein interaction networks (see Table 4.3). The degree distribution of the reconstructed Hedgehog network follows the power law distribution ($P(k) \approx k^{-\gamma}$, γ=1.75, R^2=0.93) which means that it is scale-free network (Figure 4.8). Similar to the reconstructed canonical Wnt network, the reconstructed Hedgehog signaling network also has small-world features with scale-free topology.

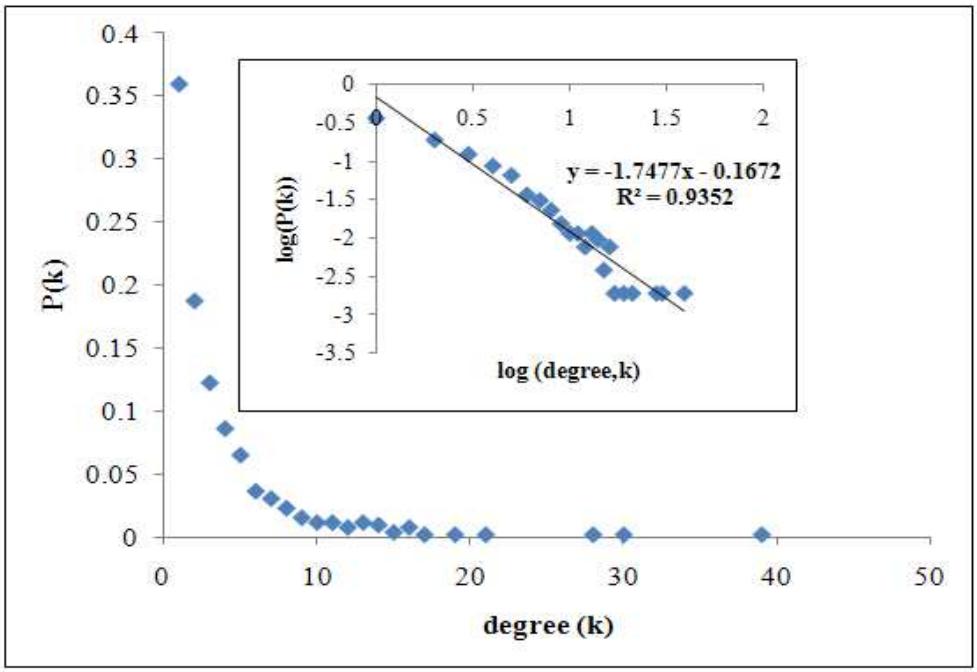


Figure 4.8. Degree distribution of the Hedgehog signaling network

The Hedgehog signaling network share the same hubs with the Wnt/β-catenin signaling network which are ci, Mer and ptc having connectivity values of 39, 30 and 28, respectively (see Appendix D, Table D.2). The transcription factor ci which is the target of Hedgehog signaling and the Hh receptor ptc are the essential proteins for Hedgehog signaling pathway. Besides, the topological analysis indicated that they are dominant in the reconstructed network. *Drosophila* protein Merlin (Mer) mainly has function in regulating the steady state levels of several signaling receptors including the Hedgehog receptor patched (ptc). The loss of it causes overactivation of the hedgehog signaling pathway (Harvey and Tapon, 2007; Kopyl *et al*., 2010).

4.2.5. Network Decomposition Analysis

The linear paths in the reconstructed Hedgehog network were also found using NetSearch algorithm of Steffen *et al*. (2002). Hedgehog (hh, ligand of Hedgehog pathway in *Drosophila*) and cubitus interruptus (ci, transcription factor of Hedgehog pathway in *Drosophila*) proteins were used as the input and the output proteins of the signaling network, respectively.

The shortest path length between wg and pan was found as 2 as the shortest 1 linear path include 3 proteins connected linearly by 2 interactions (see Table E.2). There are 428632 linear paths starting from hh leading to the transcription factor ci at the maximum 11 steps. 284 out of 568 proteins (50%) and 13 out of 17 core proteins (76%) in the reconstructed network exist in these paths.

Table 4.10. Results of the network decomposition analysis in Hedgehog signaling network

Number of steps	**Number of linear paths**	**Number of core proteins exist in the paths**	**Number of nodes exist in the paths**
2	1	3 (18%)	3 (0.5%)
3	3	5 (29%)	5 (0.9%)
4	15	10 (59%)	17 (3%)
5	47	10 (59%)	33 (6%)
6	201	12 (71%)	93 (16%)
7	878	13 (76%)	161 (28%)
8	4158	13 (76%)	211 (37%)
9	19119	13 (76%)	249 (44%)
10	91661	13 (76%)	277 (49%)
11	428632	13 (76%)	284 (50%)

As it was done for the Wnt pathway, the percentages of each protein contributing to 428632 linear paths were also found (see Table F.2). The proteins hh and ci are included in all the linear paths (100 % participation) since they are input and output proteins, respectively. Following hh and ci, the proteins having a participation percentage higher than 20% in these linear paths are also listed in Table 4.11. The receptor protein patched (ptc) having the highest participation percentage is already the essential protein of the hedgehog signaling pathway. Hh signal is transmitted to the transcription factor, ci, when the ligand hh interacts with the patched (ptc) receptor. The protein Mer which was detected as hub in the reconstructed hedgehog network has also high participation percentage in the linear paths. The other proteins (ttk, lwr and spn-A,) also have direct or indirect interactions with the ptc protein that is central to many paths in the reconstructed network. The receptors (fz2 for the wnt ligand and ptc for the hedgehog ligand) have the highest participations after the inputs and outputs in the linear paths for both wnt and hedgehog signaling protein networks.

Table 4.11. Proteins with the highest percentages in the Hedgehog linear paths

Protein	Percentage in linear paths (%)	Connectivity values
ptc (patched)	92,69	28
ttk (tramtrack)	29,84	16
lwr (lesswright)	29,72	14
Mer (merlin)	26,47	30
spn-A (spindle A)	24,74	14

4.2.6. Module Detection and Analysis

Possible modules in the reconstructed hedgehog network were also detected by utilizing MCODE. Of the 568 proteins, 49 were clustered into 9 modules (Table 4.12). Modules numbered as 1 and 2 in Table 4.12 have also been detected in the canonical wnt network.

Table 4.12. Modules detected in the reconstructed Hedgehog network

Module	Score	Nodes	Edges	Node IDs
1	3,4	9	38	E(spl), da, HLHm7, HLHm5, gro, HLHm3, HLHmdelta, HLHmbeta, HLHmgamma
2	1,8	5	10	Rpt1, Pros45, Rpt4R, Pros26.4, Rpt4
3	1,6	5	11	Rpd3, Bin1, esc, Su(z)12, E(z)
4	1,5	4	6	e(y)1, Ada2b, Rpb4, Spt3
5	1,5	4	6	aPKC, numb, par-6, baz
6	1,5	8	17	sina, ebi, CtBP, wek, dl, tamo, phyl, ttk
7	1,1	9	15	lin19, for, Nf-YA, apt, lola, BubR1, Mer, skpA, slmb
8	0,7	3	4	ptc, cact, lwr
9	0,5	2	3	Doa, spn-A

The biological significance of the molecular functions of these modules was also estimated by utilizing BİNGO. Significantly over-represented molecular function terms which are furthest down the GO hierarchy for each module are given in Table 4.13. Over-represented biological functions that the modules in the Hedgehog signaling network share are under the main categories of the GO hierarchy which are binding, catalytic activity and transcriptional activity. Furthermore, it is an important point that at least one module (module 8 in Table 4.13) has a molecular function term that is specific to the hedgehog

signaling pathway, hedgehog receptor activity. This case is also valid for the wnt pathway; the significant molecular function term of the module numbered as 6 is beta-catenin binding (see Table 4.7).

Table 4.13. Most significant molecular functions of modules in the Hedgehog network

Module	GO-ID	P-value	Description
1	43565	3,93E-13	sequence-specific DNA binding
2	16887	2,96E-08	ATPase activity
3	46976	4,55E-04	histone lysine N-methyltransferase activity (H3-K27 specific)
4	4404	6,55E-06	histone acetyltransferase activity
5	4697	2,55E-03	protein kinase C activity
6	43621	4,63E-06	protein self-association
7	4692	2,46E-03	cGMP-dependent protein kinase activity
8	8158	1,64E-03	hedgehog receptor activity
9	4712	1,46E-03	protein serine/threonine/tyrosine kinase activity

4.3. Crosstalk Analysis

477 proteins are common between the reconstructed Wnt/β-catenin (656 nodes) and Hedgehog networks (568 nodes) (See Appendix G, Table G.1). This result support the theorem that individual signaling pathways are not isolated from the other signaling pathways; contrarily they interact with each other. Besides, getting a high number of common proteins between the networks is not surprising, since the GO annotation tables of the known signaling proteins used as a selection criterion to reconstruct the wnt and hedgehog signaling networks include several common GO terms (see Table 4.14).

Table 4.14. The number of common GO terms shared by the Wnt and Hedgehog core proteins

	Wnt/β-catenin pathway	Hedgehog pathway	Number of common GO terms
Number of GO component term	37	30	19
Number of GO function term	50	52	24
Number of GO process term	220	176	73

The measurement, network crosstalk was also utilized to identify the nodes that are most likely involved in the crosstalk. The signaling proteins that have non-zero network crosstalk values are given in the Appendix G (see Table G.2). Among them, the known signaling proteins and hubs of the reconstructed wnt and hedgehog pathways are listed in Table 4.15.

Table 4.15. Proteins and network crosstalk values

Protein		**Network crosstalk value**
ci	Hub and core protein (Hedgehog)	7
Mer	Hub protein	3
ptc	Hub and core protein (Hedgehog)	3
Ubx	Core protein (Wnt)	1
sina	Core protein (Wnt)	1
cos	Core protein (Hedgehog)	1
fu	Core protein (Hedgehog)	1
sgg	Core protein (Wnt and Hedgehog)	1

Ci and ptc proteins are actually the key components of the hedgehog signaling pathway; however, it has been observed that they participate in both wnt and hedgehog networks after the reconstruction process. The protein ci is accepted to the wnt network, since it interacts with the wnt signaling core proteins which are the transmembrane receptor fz3 and the protein nej. The core proteins of the hedgehog pathway cos and fu are also added to the wnt network as they interact with ci. Furthermore, the protein ptc is included to the wnt network because of its interaction with the wnt receptor fz2 and sina that interacts with APC and promotes degradation of β-catenin (Liu *et al*., 2001). In Drosophila, the kinase protein and GSK3β homolog, shaggy (sgg), is known to have roles in both Wnt and Hedgehog signaling by regulating the phosphorylation of armadillo (arm) and ci, respectively. The detection of the proteins having non-zero network crosstalk values could be an initial and reasonable step before starting the experimental measurements for studies of the crosstalk mechanisms existing between Wnt and Hh signaling during development and cancer.

The protein cubitus interruptus (ci) which has the highest network crosstalk value can be accepted as the major crosstalk player. This finding is also consistent with the

literature: it has been indicated that activated Hedgehog signaling with Gli1 (vertebrate homolog of ci) expression generally results in reduction of nuclear β-catenin levels (He *et al*., 2006). Besides, in another study, Yanai and his colleagues (2008) showed the crosstalk between Hh and Wnt pathways in gastric cancer tissues, and observed that Gli1 overexpression suppressed Wnt signaling. As mentioned before, the hub protein Mer has roles in both wnt and hedgehog signaling pathways. The loss in the activity of Mer causes upregulation of both pathways. Although the key component of Hh signaling, Su(fu), is not among the common proteins shared by the reconstructed Wnt and Hh networks, it is an important crosstalk player according to a research performed by Meng and his colleagues (2001). They observed that Su(fu) interacts with β-catenin when there is a defect in the degradation of β-catenin. Therefore, in these situations Su(fu) can reduce the high nuclear β-catenin levels by binding to it. It means that Su(fu) overexpression can regulate Wnt signaling (Meng *et al*., 2001).

4.4. Potential Drug Targets in the Reconstructed Wnt and Hedgehog Signaling Networks

Many components of the Wnt/β-catenin and Hedgehog signaling pathways may represent targets for drug discovery efforts. As discussed in section 2.2.3, the mutations of the proteins Fzd, WIF-1, LRP5/6, GSK3β, APC, Axin and β-catenin, which are the key components of Wnt signaling in vertebrates, have been found in numerous human cancer. Thus, targeting these proteins seems to be a consequential approach in treating cancer. However, the *Drosophila* homolog of WIF-1 protein, shf, could not be included to the reconstructed Wnt/β-catenin network, since it has no interaction data. The proteins sgg (*Drosophila* homolog of vertebrate GSK3β), arr (*Drosophila* homolog of vertebrate LRP5/6), Apc and Axn, which have crucial roles in Wnt signaling pathway, got low connectivity values in the network due to their limited interaction information (Table 4.16). However, the proteins, Apc, Axn and arr had high participation percentages in the Wnt linear paths; 17,76%, 12,35% and 10,48%, respectively. The protein, arm (the *Drosophila* homolog of β-catenin), which is the key mediator of the canonical Wnt signaling had a high degree (14) in the reconstructed Wnt/β-catenin network. So, directly targeting β-catenin in cancer therapy seems to be a rational approach as also indicated in the literature (Luu *et al*., 2004). Although, they have low degrees, the frizzled receptors (fz and fz2) are

also essential for Wnt signaling network with their high participation percentages in the linear paths (Table 4.16). Therefore, the inhibition of the binding of wg to its frizzled receptors could be a rational approach in preventing cancer cell growth (resulted from excessive activation of Wnt) as also suggested in the literature (Janssens *et al*., 2006).

Although the Wnt/β-catenin signaling pathway forms one of the most attractive targets for anti-cancer strategies, at present, there is no selective inhibitor of this pathway available as a therapeutic agent. Various anti-cancer drugs have been reported so far, some of them are still under trial or have already been approved by Food and Drug Administration (FDA), but they have non-specific effects on Wnt signaling. The most distinguished among them are non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin and sulindac which reduce Wnt signaling activity indirectly. (Paul and Dey, 2008; Yanaga and Sasaguri, 2009; Gehrke *et al*., 2009).

Table 4.16. Drug targets in Wnt and Hedgehog signaling

Target protein for cancer therapy			**Activity ***		**Degree**	**Participation percentage (%)**
			Cancer	**Therapy**		
Wnt signaling	fz	Core protein (Wnt)	elavated	inhibition	4	32,10
	fz2	Core protein (Wnt)	elavated	inhibition	5	67,94
	arr (LRP5/6)	Core protein (Wnt)	elavated	inhibition	2	10,48
	sgg (GSK3β)	Core protein (Wnt), module component	reduced	activation	4	4,22
	arm (β-catenin)	Core protein (Wnt), module component	elavated	inhibition	14	100
	Apc	Core protein (Wnt), module component	reduced	activation	6	17,76
	Axn	Core protein (Wnt), module component	reduced	activation	5	12,35
Hedgehog signaling	ci (Gli)	Hub and core protein (Hedgehog)	elavated	inhibition	39	100
	ptc	Hub and core protein (Hedgehog), module component	reduced	activation	28	92,69
	smo	Core protein (Hedgehog)	elavated	inhibition	5	8,94
	hh (Shh)	Core protein (Hedgehog)	elavated	inhibition	4	100
	su(fu)	Core protein (Hedgehog)	reduced	activation	5	2,53

* see the Table 2.1 and Table 2.2 for the references

As mentioned in section 2.3.2; the vertebrate regulatory proteins of Hedgehog signaling Smo, Shh, Su(fu), Ptch1 and Gli1 could be potential drug targets in the treatment of cancer. The proteins smo and su(fu) in *Drosophila* have low degrees in the reconstructed Hedgehog network and low participation percentages in the linear paths after the graph theoretic and network decomposition analyses, respectively (Table 4.16). Further, the ligand protein hh (*Drosophila* homolog of Shh) got a low connectivity in the reconstructed Hedgehog network. The transcription factor of Hedgehog signaling, ci (*Drosophila* homolog of Gli), and the receptor protein ptc (*Drosophila* homolog of Ptch1) were detected as hub proteins after the graph theoretic analysis. Besides, the protein ptc has the highest participation percentage after the input and output proteins in the Hedgehog linear paths. The proteins ci and ptc, which were detected as essential proteins in the network, also have been identified as potential drug targets in the literature (Toftgard, 2000; Xu *et al*., 2009; Rubin and Sauvage, 2006; Kubo *et al*., 2004; Kasper *et al*., 2009). Although many components of the Hh pathway have potential to be a drug target in treating the cancer, any clinical trials have not yet been conducted for testing them (Xu *et al*., 2009).

Besides, another hub protein Mer and the proteins having high participation percentages in the linear paths (Table 4.5 and Table 4.11) could be particularly interesting drug targets (Ekman *et al*., 2006). These proteins may be considered as starting points for further experimental researches in drug design.

5. CONCLUSIONS AND RECOMMENDATIONS

Generating a global picture of a signaling pathway and its relationship with other signaling pathways allows us to intervene in diseases in which those pathways are defective. In this study, the reconstruction of Wnt/β-catenin and Hedgehog signaling pathways, whose deregulation represents potentially important mechanisms in tumour progression, was performed in *D.melanogaster* by the integration of GO annotations and interactome data. Furthermore, the following analyses were carried out to characterize the reconstructed networks: sequence similarity analysis, graph theoretical analysis, network decomposition analysis, module anlaysis and lastly crosstalk analysis. By sequence similarity analysis, the conservation of the Wnt/β-catenin and Hedgehog signaling components was investigated among different species. Next, graph theoretic analysis was performed to get an insight into the organization and structure of the reconstructed networks via topological properties. Besides, the linear paths in the reconstructed networks were investigated by network decomposition analysis to obtain detailed information about the signal transduction mechanisms. The highly interconnected regions named as modules in the reconstructed networks were also detected for a better understanding of the cellular role of these networks. In the last step, the crosstalk analysis was performed to identify the relationship between the reconstructed Wnt/β-catenin and Hedgehog signaling networks.

5.1. Conclusions

- 34 core proteins related to the Wnt/β-catenin signaling and 23 core proteins related to the Hedgehog signaling were identified in *D.melanogaster*. High amino acid identity percentages of these proteins among different species verified the literature information that Wnt/β-catenin and Hedgehog signaling pathway components are evolutionary conserved.

- Some essential direct interactions between core proteins are missing in the DroID interactome database such as the interactions between the ligands and the receptors. This

problem was solved by adding some putative interactions in *H.sapiens* to the network via homology search.

- The reconstructed Wnt/β-catenin signaling network in *D. melanogaster* consists of 656 proteins and 1253 interactions among these proteins and Hedgehog signaling network consists of 523 proteins and 945 interactions.

- The degree distribution of the reconstructed Wnt/β-catenin and Hedgehog signaling networks followed a power-law model revealing a scale-free network which is the general characteristic of complex biological networks. The network diameter and the mean path length of the reconstructed Wnt/β-catenin were found as 13 and 4.8, respectively, indicating the small-world topology. Similar to the reconstructed Wnt/β-catenin network, the reconstructed Hedgehog signaling network also has small-world features with the network diameter and the mean path length as 14 and 4.8, respectively.

- Both of the reconstructed Wnt/β-catenin and Hedgehog signaling networks share the same hubs which are ci, Mer and ptc. These proteins have great importance, since they are dominant and the less connected nodes are linked to the network via these hubs. Ci and ptc proteins are actually key components of the hedgehog signaling pathway; however, they also participate in the wnt signaling pathway by interacting with its core proteins. The protein Mer has roles in both wnt and hedgehog signaling pathways. The loss in the activity of Mer causes upregulation of both pathways.

- The linear paths starting from the ligand proteins (wg for Wnt signaling, hh for Hedgehog signaling) leading to the transcription factor proteins (pan for Wnt signaling, ci for Hedgehog signaling) at 11 steps included 61% and 50% of the proteins in the reconstructed Wnt and Hedgehog signaling networks, respectively.

- The frizzled receptors, fz and fz2, the proteins nej, ubx and dsh, which are already the essential proteins of the Wnt/β-catenin pathway, were found to be involved in the linear paths of the reconstructed Wnt/β-catenin network with high participation percentages (>30%). Besides, the receptor protein ptc, which is already the key component of the Hedgehog signaling pathway, was detected as the protein with the highest participation

percentage (92,69%) in the linear paths of the reconstructed Hedgehog network. These proteins having high participation percentages in the linear paths are indispensible since they are central to many paths in the networks.

- Many of the proteins in the modules correspond to binding proteins, cellular enzymes and transcriptional regulatory proteins for both reconstructed Wnt/β-catenin and Hedgehog signaling networks. Consequently, overrepresented biological functions, that these modules share, are under the main categories of the related GO annotation tree; binding, catalytic activity and transcriptional activity.

- Crosstalk analysis revealed that 477 proteins are common between the reconstructed Wnt/β-catenin (656 nodes) and Hedgehog network (568 nodes). This result supports the theorem that individual signaling pathways do not behave in isolation; contrarily they interact with each other.

- The protein cubitus interruptus (ci) was detected as the major crosstalk player with the highest network crosstalk value. The reports in the literature indicated that Gli1 (vertebrate homolog of ci, key component of Hedgehog signaling) overexpression suppressed Wnt signaling. This fact supports our finding that ci is a common protein between Wnt and Hedgehog signaling networks.

- It was detected that the key components of Wnt/β-catenin signaling such as WIF-1 (in *Drosophila*, shf) and GSK3β (in *Drosophila*, sgg) which are potential drug targets according to the literature did not come into prominence in the reconstructed Wnt/β-catenin network. However, having a high degree (14) in the reconstructed Wnt/β-catenin network validates the importance of the protein, β-catenin (in *Drosophila*, arm), which is the key mediator of the canonical wnt signaling. Besides, the other suggested potential drug targets in the literature, frizzled receptors, the coreceptor LRP5 (arr in *Drosophila*), APC and Axin had high participation percentages in the wnt linear paths. Thus, directly targeting these indispensible proteins in cancer therapy seems to be a rational approach as also indicated in the literature (Klaus and Birchmeier, 2008; Janssens *et al*., 2006).

- The key components of Hedgehog signaling pathway such as Smo, Shh (hh in *Drosophila*) and Su(fu) which are also suggested as potential dug targets in the literature were not detected as essential proteins due to their low degrees in the network and low participation percentages in the linear paths. On the contrary, the transcription factor of Hedgehog signaling, ci (*Drosophila* homolog of vertebrate Gli protein) and the receptor of hh ligand, ptc were detected as the hubs and central proteins in the reconstructed networks by the graph theoretic and network decomposition analyses. These proteins have also been discussed in the literature as good target proteins to repress overactivity of Hedgehog signaling in cancer cells (Toftgard, 2009; Xu *et al*., 2009; Rubin and Sauvage, 2006; Kubo *et al*., 2004; Kasper *et al*., 2009).

5.2. Recommendations

- In the reconstruction process, instead a multi-species interactome database, a comprehensive database designed specifically for any organism should be used.

- Some essential direct interactions between the core proteins of both Wnt/β-catenin and Hedgehog signaling are missing in *D.melanogaster* Interaction Database (DroID). To overcome this problem, some putative interactions in *H. sapiens* were added to the networks by homology search. Therefore, these networks should also be reconstructed in *H. sapiens* to prevent the need of adding putative interactions.

- The reconstructed large-scale protein-protein interaction networks in this study are undirected networks. Directed networks could be more helpful for understanding the crosstalk mechanism between the signaling pathways. However, the detection of the signaling proteins having non-zero network crosstalk values, which was performed in this study, could be used as an intial step in the experimental studies on the crosstalk mechanisms between Wnt/β-catenin and Hedgehog signaling.

- The hubs and central proteins in the reconstructed Wnt/β-catenin and Hedgehog networks identified by the graph theoretic and network decomposition analysis could be relatively good drug targets. These proteins may be considered as starting points for further experimental researches in drug design.

APPENDIX A: SEQUENCE SIMILARITY ANALYSIS RESULTS

Table A.1. Overall protein identity and conservation for Wnt/β-catenin signaling core proteins

name	uni name	organism	source	aa length	identity %	conservation %	domains
wg	**P09615**	**DROME**	**swiss**	**468**	**-**	**-**	**Wnt 1 domain**
WNT1	P34888	CAEEL	swiss	372	89/231 (38%)	128/231 (55%)	Wnt 1 domain
WNT1	P04628	HUMAN	swiss	370	151/262 (57%)	182/262 (69%)	Wnt 1 domain
WNT1	P04426	MOUSE	swiss	370	150/262 (57%)	182/262 (69%)	Wnt 1 domain
WNT1	P10108	XENLA	swiss	371	140/265 (52%)	179/265 (67%)	Wnt 1 domain
WNT1	P24257	DANRE	swiss	370	151/274 (55%)	187/274 (68%)	Wnt 1 domain
dally	**Q24114**	**DROME**	**swiss**	**626**	**-**	**-**	**glypican**
gpn-1	O17900	CAEEL	trembl	543	83/389 (21%)	151/389 (38%)	glypican
GPC5	P78333	HUMAN	swiss	572	140/483 (28%)	217/483 (44%)	glypican
GPC5	Q8CAL5	MOUSE	swiss	572	129/483 (26%)	213/483 (44%)	glypican
gpc4	Q5EAV3	XENLA	trembl	556	101/420 (24%)	178/420 (42%)	glypican
Zgc:171629	A7MBT1	DANRE	trembl	562	111/432 (25%)	191/432 (44%)	glypican
dlp	**Q9GPL5**	**DROME**	**trembl**	**765**	**-**	**-**	**glypican**
gpn-1	O17900	CAEEL	trembl	543	78/286 (27%)	148/286 (51%)	glypican
GPC4	O75487	HUMAN	swiss	556	141/333 (42%)	209/333 (62%)	glypican
GPC6	Q9R087	MOUSE	swiss	765	142/326 (43%)	203/326 (62%)	glypican
Xgly4	Q8AYR4	XENLA	trembl	556	142/351 (40%)	212/351 (60%)	glypican
Zgc:171629	A7MBT1	DANRE	trembl	562	151/370 (40%)	216/370 (58%)	glypican
por	**Q9VWV9**	**DROME**	**swiss**	**525**	**-**	**-**	**MBOAT**
mom-1	Q22329	CAEEL	trembl	442	96/342 (28%)	162/342 (47%)	MBOAT
PORCN	Q9H237	HUMAN	swiss	461	149/481 (30%)	230/481 (47%)	MBOAT
Porcn	Q9JJJ7	MOUSE	swiss	461	149/481 (30%)	230/481 (47%)	MBOAT
porcn	Q9I935	XENLA	trembl	461	153/484 (31%)	239/484 (49%)	MBOAT
Zgc:55392	Q803X3	DANRE	trembl	449	150/485 (30%)	244/485 (50%)	MBOAT
fz	**P18537**	**DROME**	**swiss**	**581**	**-**	**-**	**FZ**
mom-5	O16147	CAEEL	trembl	568	214/560 (38%)	317/560 (56%)	FZ
FZD1	Q9UP38	HUMAN	swiss	647	269/548 (49%)	345/548 (62%)	FZ
FZD7	Q61090	MOUSE	swiss	574	266/543 (48%)	344/543 (63%)	FZ
fzd1	Q9I9M5	XENLA	swiss	559	267/540 (49%)	350/540 (64%)	FZ
fzd7a	Q7SZR7	DANRE	trembl	559	272/540 (50%)	353/540 (65%)	FZ
fz2	**Q9VVX3**	**DROME**	**swiss**	**694**	**-**	**-**	**FZ**
cfz-2	Q9U8U6	CAEEL	trembl	550	233/595 (39%)	325/595 (54%)	FZ
FZD5	Q13467	HUMAN	swiss	585	320/574 (55%)	378/574 (65%)	FZ
FZD5	Q9EQD0	MOUSE	swiss	585	320/567 (56%)	377/567 (66%)	FZ
fzd8	O93274	XENLA	swiss	581	325/611 (53%)	392/611 (64%)	FZ
fzd8a	Q9YI00	DANRE	trembl	579	313/563 (55%)	378/563 (67%)	FZ
fz3	**O77438**	**DROME**	**swiss**	**581**	**-**	**-**	**FZ**
lin-17	Q95Y45	CAEEL	trembl	556	140/505 (27%)	213/505 (42%)	FZ
FZD10	Q9ULW2	HUMAN	swiss	581	156/517 (30%)	248/517 (47%)	FZ
Fzd5	Q9EQD0	MOUSE	swiss	585	153/518 (29%)	235/518 (45%)	FZ
fzd5	P58421	XENLA	swiss	559	151/526 (28%)	227/526 (43%)	FZ
fzd10	Q9W6E3	DANRE	trembl	580	159/519 (30%)	256/519 (49%)	FZ

Table A.1. Overall protein identity and conservation for Wnt/β-catenin signaling core proteins-continued

name	uni name	organism	source	aa length	identity %	conservation %	domains
fz4	**Q9NBW1**	**DROME**	**swiss**	**705**	**-**	**-**	**FZ**
mom-5	O16147	CAEEL	trembl	568	159/565 (28%)	244/565 (43%)	FZ
FZD4	Q9ULV1	HUMAN	swiss	537	182/523 (34%)	275/523 (52%)	FZ
Fzd4	Q61088	MOUSE	swiss	537	185/532 (34%)	275/532 (51%)	FZ
fzd10-B	Q9W742	XENLA	swiss	580	164/540 (30%)	252/540 (46%)	FZ
fzd10	Q9W6E3	DANRE	trembl	580	162/542 (29%)	257/542 (47%)	FZ
G-oalpha47A	**P16378**	**DROME**	**swiss**	**354**	**-**	**-**	**G-alpha**
goa-1	P51875	CAEEL	swiss	354	308/354 (87%)	329/354 (92%)	G-alpha
GNAO1	P09471	HUMAN	swiss	354	291/354 (82%)	318/354 (89%)	G-alpha
Gnao1	P18872	MOUSE	swiss	354	287/354 (81%)	316/354 (89%)	G-alpha
gna0	P10825	XENLA	swiss	354	281/354 (79%)	313/354 (88%)	G-alpha
gnao1	Q6PBP1	DANRE	trembl	354	285/354 (80%)	317/354 (89%)	G-alpha
arr (arrow)	**Q95V09**	**DROME**	**trembl**	**1678**	**-**	**-**	**EGF_like, LDL receptor class A**
lrp-1	Q04833	CAEEL	swiss	4753	386/1453 (26%)	632/1453 (43%)	EGF_like, LDL receptor class A
LRP6	O75581	HUMAN	swiss	1613	703/1637 (42%)	987/1637 (60%)	EGF_like, LDL receptor class A
LRP6	O88572	MOUSE	swiss	1613	709/1637 (43%)	989/1637 (60%)	EGF_like, LDL receptor class A
lrp5	Q8AYF1	XENLA	trembl	1605	702/1643 (42%)	984/1643 (59%)	EGF_like, LDL receptor class A
lrp6	B5L5I6	DANRE	trembl	1620	693/1650 (42%)	968/1650 (58%)	EGF_like, LDL receptor class A
dsh	**P51140**	**DROME**	**swiss**	**623**	-	**-**	**DIX, PDZ, DEP**
mig-5	Q22227	CAEEL	trembl	672	95/300 (31%)	148/300 (49%)	DIX, PDZ, DEP
DVL-3	Q92997	HUMAN	swiss	716	277/548 (50%)	354/548 (64%)	DIX, PDZ, DEP
DVL-3	Q61062	MOUSE	swiss	716	277/548 (50%)	356/548 (64%)	DIX, PDZ, DEP
DVL-3	Q6DKE2	XENLA	swiss	717	283/571 (49%)	368/571 (64%)	DIX, PDZ, DEP
dvl2	Q803Q5	DANRE	trembl	747	276/565 (48%)	355/565 (62%)	DIX, PDZ, DEP
nkd	**Q9VVV9**	**DROME**	**swiss**	**928**	**-**	**-**	**EF-hand**
NCS1	P36608	CAEEL	swiss	191	23/66 (34%)	39/66 (59%)	EF-hand
NKD1	Q969G9	HUMAN	swiss	470	32/88 (36%)	56/88 (63%)	EF-hand
NKD1	Q99MH6	MOUSE	swiss	471	34/88 (38%)	57/88 (64%)	EF-hand
NCS-1	Q91614	XENLA	swiss	190	24/66 (36%)	41/66 (62%)	EF-hand
NKD1	Q2TJA6	DANRE	swiss	440	30/76 (39%)	49/76 (64%)	EF-hand
Apc	**P91667**	**DROME**	**trembl**	**2416**	**-**	**-**	**ARM_REPEAT**
apr-1	Q21227	CAEEL	swiss	1188	91/288 (31%)	148/288 (51%)	ARM_REPEAT
APC	P25054	HUMAN	swiss	2843	263/496 (53%)	339/496 (68%)	ARM_REPEAT
Apc	Q61315	MOUSE	swiss	2845	263/496 (53%)	340/496 (68%)	ARM_REPEAT
APC	P70039	XENLA	swiss	2829	255/479 (53%)	330/479 (68%)	ARM_REPEAT
apc	**-**	DANRE	**-**	2754	256/479 (53%)	330/479 (68%)	ARM_REPEAT
Apc2	**Q9Y1T2**	**DROME**	**trembl**	**1067**	**-**	**-**	**ARM_REPEAT**
apr-1	Q21227	CAEEL	swiss	1188	94/292 (32%)	147/292 (50%)	ARM_REPEAT
APC variant	Q4LE70	HUMAN	trembl	2845	210/427 (49%)	280/427 (65%)	ARM_REPEAT
Apc	Q61315	MOUSE	swiss	2845	208/427 (48%)	281/427 (65%)	ARM_REPEAT
apc	P70039	XENLA	swiss	2829	199/410 (48%)	270/410 (65%)	ARM_REPEAT
apc	**-**	DANRE	**-**	2754	205/427 (48%)	277/427 (64%)	ARM_REPEAT
Axn	**Q9V407**	**DROME**	**swiss**	**745**	**-**	**-**	**DIX domain, RGS domain**
pry-1	O62090	CAEEL	swiss	586	38/139 (27%)	65/139 (46%)	DIX domain, RGS domain
AXIN1	O15169	HUMAN	swiss	862	93/328 (28%)	134/328 (40%)	DIX domain, RGS domain
Axin1	O35625	MOUSE	swiss	863	93/323 (28%)	135/323 (41%)	DIX domain, RGS domain
axin1	Q9YGY0	XENLA	swiss	842	72/230 (31%)	106/230 (46%)	DIX domain, RGS domain
axin1	P57094	DANRE	swiss	835	72/236 (30%)	103/236 (43%)	DIX domain, RGS domain

Table A.1. Overall protein identity and conservation for Wnt/β-catenin signaling core proteins-continued

name	uni name	organism	source	aa length	identity %	conservation %	domains
sgg	**P18431**	**DROME**	**swiss**	**1067**	**-**	**-**	**Protein kinase**
gsk-3	Q9U2Q9	CAEEL	swiss	362	242/330 (73%)	280/330 (84%)	Protein kinase
GSK3B	P49841	HUMAN	swiss	420	295/375 (78%)	330/375 (88%)	Protein kinase
Gsk3b	Q9WV60	MOUSE	swiss	420	294/367 (80%)	327/367 (89%)	Protein kinase
gsk3b	Q91757	XENLA	trembl	420	290/357 (81%)	321/357 (89%)	Protein kinase
gsk3b	Q9YH60	DANRE	trembl	421	297/378 (78%)	333/378 (88%)	Protein kinase
slmb	**Q9VDE3**	**DROME**	**trembl**	**510**	**-**	**-**	**FBOX domain**
lin-23	Q09990	CAEEL	swiss	665	319/499 (63%)	379/499 (75%)	FBOX domain
BTRC	Q9Y297	HUMAN	swiss	605	390/485 (80%)	434/485 (89%)	FBOX domain
Btrc	Q3ULA2	MOUSE	trembl	605	393/504 (77%)	440/504 (87%)	FBOX domain
TRCB	Q91854	XENLA	swiss	518	395/489 (80%)	437/489 (89%)	FBOX domain
fbxw11b	Q6PGW4	DANRE	trembl	527	376/475 (79%)	425/475 (89%)	FBOX domain
CkIalpha	**P54367**	**DROME**	**swiss**	**337**	**-**	**-**	**Protein kinase**
kin-19	P42168	CAEEL	swiss	341	239/305 (78%)	268/305 (87%)	Protein kinase
CSNK1A1	P48729	HUMAN	swiss	337	253/330 (76%)	281/330 (85%)	Protein kinase
Csnk1a1	Q8BK63	MOUSE	swiss	337	253/330 (76%)	281/330 (85%)	Protein kinase
csnk1a1	P67963	XENLA	swiss	337	253/330 (76%)	281/330 (85%)	Protein kinase
csnk1a1	Q8JGT0	DANRE	trembl	325	246/301 (81%)	272/301 (90%)	Protein kinase
arm	**P18824**	**DROME**	**swiss**	**843**	**-**	**-**	**ARM_REPEAT**
bar-1	Q18825	CAEEL	swiss	811	149/543 (27%)	250/543 (46%)	ARM_REPEAT
CTNNB1	P35222	HUMAN	swiss	781	551/816 (67%)	638/816 (78%)	ARM_REPEAT
Catenin beta-1	Q02248	MOUSE	swiss	781	551/816 (67%)	638/816 (78%)	ARM_REPEAT
beta-catenin	P26233	XENLA	swiss	781	550/816 (67%)	639/816 (78%)	ARM_REPEAT
ctnnb1	Q7ZU14	DANRE	trembl	780	548/815 (67%)	635/815 (77%)	ARM_REPEAT
lgs	**Q961D9**	**DROME**	**swiss**	**1469**	**-**	**-**	**ND**
		CAEEL		No significant similarity found			
BCL9	O00512	HUMAN	swiss	1426	36/122 (29%)	52/122 (42%)	ND
Bcl9	Q9D219	MOUSE	swiss	1425	16/29 (55%)	25/29 (86%)	ND
bcl9	Q6NRE2	XENLA	trembl	796	26/82 (31%)	40/82 (48%)	ND
bcl9l	Q67FY3	DANRE	swiss	1530	19/63 (30%)	33/63 (52%)	ND
pygo	**Q9V9W8**	**DROME**	**swiss**	**815**	**-**	**-**	**PHD-type zinc finger**
C17G1.4a	Q93238	CAEEL	trembl	925	13/56 (23%)	20/56 (35%)	PHD-type zinc finger
PYGO2	Q9BRQ0	HUMAN	swiss	406	31/68 (45%)	44/68 (64%)	PHD-type zinc finger
Pygo2	Q80V76	MOUSE	trembl	405	31/68 (45%)	44/68 (64%)	PHD-type zinc finger
Pygopus-2alpha	Q8AXY8	XENLA	trembl	389	33/68 (48%)	47/68 (69%)	PHD-type zinc finger
pygo2	Q1L8T6	DANRE	trembl	571	31/68 (45%)	45/68 (66%)	PHD-type zinc finger
pan	**P91943**	**DROME**	**swiss**	**751**	**-**	**-**	**HMG box DNA binding**
pop-1	Q10666	CAEEL	swiss	438	59/119 (49%)	85/119 (71%)	HMG box DNA binding
TCF7L2	Q9NQB0	HUMAN	swiss	619	148/318 (46%)	181/318 (56%)	HMG box DNA binding
Tcf7l2	Q924A0	MOUSE	swiss	459	133/287 (46%)	162/287 (56%)	HMG box DNA binding
tcf7l1-A	P70062	XENLA	swiss	554	163/416 (39%)	206/416 (49%)	HMG box DNA binding
tcf7l1b	Q800Q5	DANRE	swiss	551	132/292 (45%)	157/292 (53%)	HMG box DNA binding
gro	**P16371**	**DROME**	**swiss**	**730**	**-**	**-**	**CCN domain, WD_REPEATS**
unc-37	O02482	CAEEL	swiss	612	199/355 (56%)	257/355 (72%)	CCN domain, WD_REPEATS
TLE3	Q04726	HUMAN	swiss	772	491/798 (61%)	568/798 (71%)	CCN domain, WD_REPEATS
Tle4	Q62441	MOUSE	swiss	773	485/800 (60%)	561/800 (70%)	CCN domain, WD_REPEATS
tle4	O42478	XENLA	swiss	772	471/780 (60%)	539/780 (69%)	WD_REPEATS
gro2	O13166	DANRE	swiss	761	485/795 (61%)	558/795 (70%)	CCN domain, WD_REPEATS

Table A.1. Overall protein identity and conservation for Wnt/β-catenin signaling core proteins-continued

name	uni name	organism	source	aa length	identity %	conservation %	domains
nej	**Q9W321**	**DROME**	**trembl**	**3276**	**-**	**-**	**KIX domain, bromo domain**
cbp-1	P34545	CAEEL	swiss	2056	418/826 (50%)	543/826 (65%)	KIX domain, bromo domain
CREBBP	Q92793	HUMAN	swiss	2442	571/817 (69%)	657/817 (80%)	KIX domain, bromo domain
Crebbp	P45481	MOUSE	swiss	2441	607/1123 (54%)	726/1123 (64%)	KIX domain, bromo domain
LOC495689	Q5U248	XENLA	trembl	2428	559/836 (66%)	648/836 (77%)	KIX domain, bromo domain
crebbpa	A3KQN2	DANRE	trembl	2111	590/991 (59%)	697/991 (70%)	KIX domain, bromo domain
lin19	**Q24311**	**DROME**	**swiss**	**774**	**-**	**-**	**CULLIN**
cul-1	Q17389	CAEEL	swiss	780	333/792 (42%)	486/792 (61%)	CULLIN
CUL1	Q13616	HUMAN	swiss	776	489/779 (62%)	595/779 (76%)	CULLIN
Cul1	Q9WTX6	MOUSE	trembl	776	493/789 (62%)	599/789 (75%)	CULLIN
MGC114992	Q4V7X4	XENLA	trembl	776	491/789 (62%)	598/789 (75%)	CULLIN
cul1b	Q802D4	DANRE	trembl	774	493/787 (62%)	597/787 (75%)	CULLIN
skpC	**Q9VWC4**	**DROME**	**trembl**	**162**	**-**	**-**	**Skp1**
skr-1	Q93647	CAEEL	trembl	176	70/153 (45%)	95/153 (62%)	Skp1
SKP1	P63208	HUMAN	swiss	163	125/163 (76%)	142/163 (87%)	Skp1
Skp1	Q9WTX5	MOUSE	swiss	163	82/145 (56%)	103/145 (71%)	Skp1
skp1	Q71U00	XENLA	swiss	163	81/145 (55%)	103/145 (71%)	Skp1
skp1	Q6PBY8	DANRE	trembl	163	81/145 (55%)	103/145 (71%)	Skp1
sina	**P21461**	**DROME**	**swiss**	**314**			**Znf_RING, Znf_SIAH**
sia-1	Q965X6	CAEEL	swiss	339	187/273 (68%)	219/273 (80%)	Znf_RING, Znf_SIAH
SIAH1	Q8IUQ4	HUMAN	swiss	282	213/269 (79%)	230/269 (85%)	Znf_RING, Znf_SIAH
Siah1b	Q06985	MOUSE	swiss	282	215/280 (76%)	232/280 (82%)	Znf_RING, Znf_SIAH
siah2	Q9I8X5	XENLA	swiss	313	202/248 (81%)	219/248 (88%)	Znf_RING, Znf_SIAH
siah1	Q7ZVG6	DANRE	swiss	282	215/288 (74%)	240/288 (83%)	Znf_RING, Znf_SIAH
Psn	**O02194**	**DROME**	**swiss**	**541**	**-**	**-**	**Presenilin**
sel-12	P52166	CAEEL	swiss	444	228/450 (50%)	300/450 (66%)	Presenilin
PSEN1	P49768	HUMAN	swiss	467	237/447 (53%)	301/447 (67%)	Presenilin
Psen2	Q61144	MOUSE	swiss	448	154/253 (60%)	195/253 (77%)	Presenilin
psen1	O12976	XENLA	swiss	433	235/448 (52%)	299/448 (66%)	Presenilin
psen1	Q9W6T7	DANRE	swiss	456	234/448 (52%)	295/448 (65%)	Presenilin
pont	**Q9VH07**	**DROME**	**swiss**	**456**	**-**	**-**	**ATPases**
ruvb-2	Q9GZH2	CAEEL	trembl	448	185/453 (40%)	281/453 (62%)	ATPases
RUVBL1	B2R5S0	HUMAN	trembl	456	362/455 (79%)	416/455 (91%)	ATPases
Ruvbl1	Q3U1C2	MOUSE	trembl	456	361/455 (79%)	416/455 (91%)	ATPases
ruvbl1	Q9DE26	XENLA	swiss	456	366/455 (80%)	417/455 (91%)	ATPases
ruvbl1	Q8AWW7	DANRE	swiss	456	362/455 (79%)	416/455 (91%)	ATPases
Tak1	**Q9V3Q6**	**DROME**	**swiss**	**678**	**-**	**-**	**Protein kinase**
mom-4	Q9XTC6	CAEEL	swiss	536	69/242 (28%)	128/242 (52%)	Protein kinase
MAP3K7	O43318	HUMAN	swiss	606	154/285 (54%)	199/285 (69%)	Protein kinase
Map3k7	Q62073	MOUSE	swiss	579	154/285 (54%)	199/285 (69%)	Protein kinase
map3k7	O73613	XENLA	trembl	616	152/272 (55%)	196/272 (72%)	Protein kinase
map3k7	Q503G7	DANRE	trembl	544	144/274 (52%)	194/274 (70%)	Protein kinase
nmo	**Q8T030**	**DROME**	**trembl**	**414**	**-**	**-**	**Protein kinase**
lit-1	Q9U9Y8	CAEEL	trembl	454	254/400 (63%)	316/400 (79%)	Protein kinase
NLK	Q9UBE8	HUMAN	swiss	515	301/375 (80%)	341/375 (90%)	Protein kinase
Nlk	O54949	MOUSE	swiss	515	301/375 (80%)	341/375 (90%)	Protein kinase
nlk.2	Q8QGV6	XENLA	swiss	447	301/401 (75%)	342/401 (85%)	Protein kinase
nlk2	B3IWJ8	DANRE	trembl	452	303/375 (80%)	342/375 (91%)	Protein kinase

Table A.1. Overall protein identity and conservation for Wnt/β-catenin signaling core proteins-continued

name	uni name	organism	source	aa length	identity %	conservation %	domains
shf	**Q9W3W5**	**DROME**	**swiss**	**456**	**-**	**-**	**WIF, EGF-like**
apx-1	P41990	CAEEL	swiss	515	52/169 (30%)	81/169 (47%)	WIF, EGF-like
WIF1	Q9Y5W5	HUMAN	swiss	379	112/338 (33%)	167/338 (49%)	WIF, EGF-like
Wif1	Q9WUA1	MOUSE	swiss	379	112/337 (33%)	167/337 (49%)	WIF, EGF-like
wif1	Q9W6F8	XENLA	swiss	374	111/338 (32%)	172/338 (50%)	WIF, EGF-like
wif1	Q9W6F9	DANRE	swiss	378	117/340 (34%)	174/340 (51%)	WIF, EGF-like
Med	**O62609**	**DROME**	**trembl**	**771**	**-**	**-**	**MH**
sma-4	P45897	CAEEL	swiss	570	109/224 (48%)	142/224 (63%)	MH
SMAD4	Q13485	HUMAN	swiss	552	201/309 (65%)	221/309 (71%)	MH
Smad4	P97471	MOUSE	swiss	551	200/307 (65%)	222/307 (72%)	MH
smad4	Q9W639	XENLA	trembl	549	203/314 (64%)	225/314 (71%)	MH
Smad4	B1PS58	DANRE	trembl	547	184/235 (78%)	201/235 (85%)	MH
Smox	**O96660**	**DROME**	**trembl**	**486**	**-**	**-**	**MH**
sma-2	Q02330	CAEEL	swiss	418	118/201 (58%)	142/201 (70%)	MH
SMAD2	Q15796	HUMAN	swiss	467	295/526 (56%)	342/526 (65%)	MH
Smad3	Q8BUN5	MOUSE	swiss	425	297/487 (60%)	349/487 (71%)	MH
Mad2	Q32N71	XENLA	trembl	467	299/526 (56%)	346/526 (65%)	MH
smad3a	Q8AY15	DANRE	trembl	425	297/487 (60%)	347/487 (71%)	MH

Table A.2. Overall protein identity and conservation for Hedgehog signaling core proteins

name	uni name	organism	source	aa length	identity %	positives %	domains
Ttv	**Q9V730**	**DROME**	**swiss**	**760**	**100**	**100**	**ExostosinGlyco_transf_64**
EXT1	O01704	CAEEL	swiss	378	170/351 (48%)	233/351 (66%)	Exostosin
EXT1	Q16394	HUMAN	swiss	746	412/776 (53%)	527/776 (67%)	ExostosinGlyco_transf_64
Extl1	Q9JKV7	MOUSE	swiss	669	270/706 (38%)	388/706 (54%)	ExostosinGlyco_transf_64
ext1	Q52KD9	XENLA	trembl	738	405/766 (52%)	519/766 (67%)	ExostosinGlyco_transf_64
ext1a	Q5IGR8	DANRE	swiss	730	410/773 (53%)	517/773 (66%)	ExostosinGlyco_transf_64
disp	**Q9VNJ5**	**DROME**	**swiss**	**1218**	**100**	**100**	**SSD**
ptd-2	Q19153	CAEEL	trembl	936	136/528 (25%)	237/528 (44%)	SSD
DISP1	Q96F81	HUMAN	swiss	1524	325/945 (34%)	519/945 (54%)	SSD
Disp1	Q3TDN0	MOUSE	swiss	1521	340/1000 (34%)	542/1000 (54%)	SSD
ptch2	Q9DEF3	XENLA	trembl	1413	27/123 (21%)	65/123 (52%)	SSD
disp1	Q6R5J2	DANRE	swiss	1464	318/944 (33%)	519/944 (54%)	SSD
ski(rasp)	**Q9VZU2**	**DROME**	**swiss**	**500**	**100**	**100**	**MBOAT**
hhat-1	Q7YSJ3	CAEEL	trembl	519	105/403 (26%)	186/403 (46%)	MBOAT
HHAT	Q05BM0	HUMAN	trembl	471	88/305 (28%)	143/305 (46%)	MBOAT
Hhat	Q8BMT9	MOUSE	swiss	499	88/310 (28%)	140/310 (45%)	MBOAT
hhatl	Q7ZYD3	XENLA	trembl	503	57/247 (23%)	106/247 (42%)	MBOAT
hhat	A8WG41	DANRE	trembl	494	80/282 (28%)	140/282 (49%)	MBOAT
dally	**Q24114**	**DROME**	**swiss**	**626**	**100**	**100**	**Glypican**
gpn-1	O17900	CAEEL	trembl	543	83/389 (21%)	151/389 (38%)	Glypican
GPC5	P78333	HUMAN	swiss	572	140/483 (28%)	217/483 (44%)	Glypican
GPC5	Q8CAL5	MOUSE	swiss	572	129/483 (26%)	213/483 (44%)	Glypican
gpc4	Q5EAV3	XENLA	trembl	556	101/420 (24%)	178/420 (42%)	Glypican
Zgc:171629	A7MBT1	DANRE	trembl	562	111/432 (25%)	191/432 (44%)	Glypican
dlp	**Q9GPL5**	**DROME**	**trembl**	**765**	**100**	**100**	**Glypican**
gpn-1	O17900	CAEEL	trembl	543	78/286 (27%)	148/286 (51%)	Glypican
GPC4	O75487	HUMAN	swiss	556	141/333 (42%)	209/333 (62%)	Glypican
GPC6	Q9R087	MOUSE	swiss	765	142/326 (43%)	203/326 (62%)	Glypican
Xgly4	Q8AYR4	XENLA	trembl	556	142/351 (40%)	212/351 (60%)	Glypican
Zgc:171629	A7MBT1	DANRE	trembl	562	151/370 (40%)	216/370 (58%)	Glypican
Rfabg	**Q9V496**	**DROME**	**swiss**	**3351**	**100**	**100**	**VitellogeninVWFD**
vit-5	P06125	CAEEL	swiss	1603	209/974 (21%)	383/974 (39%)	VitellogeninVWFD
APOB	P04114	HUMAN	swiss	4563	195/893 (21%)	360/893 (40%)	Vitellogenin
Apob	Q8CGG8	MOUSE	trembl	1477	191/874 (21%)	361/874 (41%)	Vitellogenin
VITA2	P18709	XENLA	swiss	1807	185/907 (20%)	347/907 (38%)	VitellogeninVWFD
apobl	Q5TZ29	DANRE	trembl	3730	178/854 (20%)	353/854 (41%)	Vitellogenin
shf	**Q9W3W5**	**DROME**	**swiss**	**456**	**100**	**100**	**WIF EGF-like**
apx-1	P41990	CAEEL	swiss	515	52/169 (30%)	81/169 (47%)	WIF EGF-like
WIF1	Q9Y5W5	HUMAN	swiss	379	112/338 (33%)	167/338 (49%)	WIF EGF-like
Wif1	Q9WUA1	MOUSE	swiss	379	112/337 (33%)	167/337 (49%)	WIF EGF-like
wif1	Q9W6F8	XENLA	swiss	374	111/338 (32%)	172/338 (50%)	WIF EGF-like
wif1	Q9W6F9	DANRE	swiss	378	117/340 (34%)	174/340 (51%)	WIF EGF-like

Table A.2. Overall protein identity and conservation for Hedgehog signaling core proteins-continued

name	uni name	organism	source	aa length	identity %	conservation %	domains
hh	**Q02936**	**DROME**	**swiss**	**471**	**100**	**100**	**HH_signal**
wrt-1	Q94128	CAEEL	swiss	485	44/161 (27%)	90/161 (55%)	Hint
DHH	O43323	HUMAN	swiss	396	195/389 (50%)	253/389 (65%)	HH_signal
Dhh	Q61488	MOUSE	swiss	396	194/389 (49%)	253/389 (65%)	HH_signal
SHH	Q92000	XENLA	swiss	444	191/432 (44%)	263/432 (60%)	HH_signal
twhh	Q90419	DANRE	swiss	416	193/405 (47%)	263/405 (64%)	HH_signal
smo	**P91682**	**DROME**	**swiss**	**1036**	**100**	**100**	**FZ**
cfz-2	Q3LTR6	CAEEL	trembl	578	73/277 (26%)	137/277 (49%)	FZ
SMO	Q99835	HUMAN	swiss	787	248/580 (42%)	370/580 (63%)	FZ
Smo	P56726	MOUSE	swiss	793	245/580 (42%)	369/580 (63%)	FZ
smo	Q98SW5	XENLA	trembl	814	244/580 (42%)	375/580 (64%)	FZ
smo	Q90X26	DANRE	trembl	822	245/566 (43%)	369/566 (65%)	FZ
ptc	**P18502**	**DROME**	**swiss**	**1286**	**100**	**100**	**SSD**
ptc-1	Q09614	CAEEL	swiss	1408	279/852 (32%)	471/852 (55%)	SSD
PTCH2	Q9Y6C5	HUMAN	swiss	1203	423/1144 (36%)	654/1144 (57%)	SSD
Ptch2	O35595	MOUSE	swiss	1182	413/1075 (38%)	623/1075 (57%)	SSD
ptch1	Q98SW6	XENLA	trembl	1418	469/1174 (39%)	697/1174 (59%)	SSD
ptch1	Q98864	DANRE	swiss	1220	245/607 (40%)	374/607 (61%)	SSD
cos	**O16844**	**DROME**	**swiss**	**1201**	**100**	**100**	**Kinesin-motor**
osm-3	P46873	CAEEL	swiss	699	83/290 (28%)	140/290 (48%)	Kinesin-motor
KIF27	Q86VH2	HUMAN	swiss	1401	89/303 (29%)	149/303 (49%)	Kinesin-motor
Kif27	Q7M6Z4	MOUSE	swiss	1394	92/303 (30%)	153/303 (50%)	Kinesin-motor
kif4	Q91784	XENLA	swiss	1226	95/300 (31%)	145/300 (48%)	Kinesin-motor
kif7	Q58G59	DANRE	swiss	1363	124/449 (27%)	221/449 (49%)	Kinesin-motor
slmb	**Q9VDE3**	**DROME**	**trembl**	**510**	**100**	**100**	**FBOX domain**
lin-23	Q09990	CAEEL	swiss	665	319/499 (63%)	379/499 (75%)	FBOX domain
BTRC	Q9Y297	HUMAN	swiss	605	390/485 (80%)	434/485 (89%)	FBOX domain
Btrc	Q3ULA2	MOUSE	trembl	605	393/504 (77%)	440/504 (87%)	FBOX domain
TRCB	Q91854	XENLA	swiss	518	395/489 (80%)	437/489 (89%)	FBOX domain
fbxw11b	Q6PGW4	DANRE	trembl	527	376/475 (79%)	425/475 (89%)	FBOX domain
sgg	**P18431**	**DROME**	**swiss**	**1067**	**100**	**100**	**Protein kinase**
gsk-3	Q9U2Q9	CAEEL	swiss	362	242/330 (73%)	280/330 (84%)	Protein kinase
GSK3B	P49841	HUMAN	swiss	420	295/375 (78%)	330/375 (88%)	Protein kinase
Gsk3b	Q9WV60	MOUSE	swiss	420	294/367 (80%)	327/367 (89%)	Protein kinase
gsk3b	Q91757	XENLA	trembl	420	290/357 (81%)	321/357 (89%)	Protein kinase
gsk3b	Q9YH60	DANRE	trembl	421	297/378 (78%)	333/378 (88%)	Protein kinase
CkIalpha	**P54367**	**DROME**	**swiss**	**337**	**100**	**100**	**Protein kinase**
kin-19	P42168	CAEEL	swiss	341	239/305 (78%)	268/305 (87%)	Protein kinase
CSNK1A1	P48729	HUMAN	swiss	337	253/330 (76%)	281/330 (85%)	Protein kinase
Csnk1a1	Q8BK63	MOUSE	swiss	337	253/330 (76%)	281/330 (85%)	Protein kinase
csnk1a1	P67963	XENLA	swiss	337	253/330 (76%)	281/330 (85%)	Protein kinase
csnk1a1	Q8JGT0	DANRE	trembl	325	246/301 (81%)	272/301 (90%)	Protein kinase

Table A.2. Overall protein identity and conservation for Hedgehog signaling core proteins-continued

name	uni name	organism	source	aa length	identity %	conservation %	domains
Pka-C1	**P12370**	**DROME**	**swiss**	**353**	**100**	**100**	**Protein kinaseAGC-kinase C-terminal**
kin-1	P21137	CAEEL	swiss	404	266/357 (74%)	298/357 (83%)	Protein kinase
PRKACA	P17612	HUMAN	swiss	351	291/353 (82%)	317/353 (89%)	Protein kinaseAGC-kinase C-terminal
Prkaca	P05132	MOUSE	swiss	351	288/353 (81%)	315/353 (89%)	Protein kinaseAGC-kinase C-terminal
prkacb	Q7ZWV0	XENLA	trembl	351	295/353 (83%)	324/353 (91%)	Protein kinaseAGC-kinase C-terminal
prkacaa	A3KMS9	DANRE	trembl	352	289/353 (81%)	319/353 (90%)	Protein kinaseAGC-kinase C-terminal
Roc1a	**Q9W5E1**	**DROME**	**swiss**	**108**	**100**	**100**	**RING-type zinc finger**
rbx-1	Q23457	CAEEL	swiss	110	84/105 (80%)	92/105 (87%)	RING-type zinc finger
RBX1	P62877	HUMAN	swiss	108	92/101 (91%)	96/101 (95%)	RING-type zinc finger
Rbx1	P62878	MOUSE	swiss	108	92/101 (91%)	96/101 (95%)	RING-type zinc finger
rnf7	Q6NU82	XENLA	trembl	96	44/88 (50%)	57/88 (64%)	RING-type zinc finger
rbx1	Q32Q48	DANRE	trembl	122	92/101 (91%)	96/101 (95%)	RING-type zinc finger
lin19	**Q24311**	**DROME**	**swiss**	**774**	**100**	**100**	**CULLIN**
cul-1	Q17389	CAEEL	swiss	780	333/792 (42%)	486/792 (61%)	CULLIN
CUL1	Q13616	HUMAN	swiss	776	489/779 (62%)	595/779 (76%)	CULLIN
Cul1	Q9WTX6	MOUSE	trembl	776	493/789 (62%)	599/789 (75%)	CULLIN
MGC114992	Q4V7X4	XENLA	trembl	776	491/789 (62%)	598/789 (75%)	CULLIN
cul1b	Q802D4	DANRE	trembl	774	493/787 (62%)	597/787 (75%)	CULLIN
Gprk2	**P32866**	**DROME**	**swiss**	**714**	**100**	**100**	**RGSProtein kinaseAGC-kinase C-terminal**
grk-1	Q09537	CAEEL	swiss	642	275/438 (62%)	335/438 (76%)	RGSProtein kinaseAGC-kinase C-terminal
GRK5	P34947	HUMAN	swiss	590	306/434 (70%)	357/434 (82%)	RGSProtein kinaseAGC-kinase C-terminal
Grk5	Q8VEB1	MOUSE	swiss	590	317/472 (67%)	378/472 (80%)	RGSProtein kinaseAGC-kinase C-terminal
grk4	Q6DCW4	XENLA	trembl	575	294/422 (69%)	351/422 (83%)	RGSProtein kinaseAGC-kinase C-terminal
zgc:153020	Q08CJ6	DANRE	trembl	573	292/439 (66%)	349/439 (79%)	RGSProtein kinaseAGC-kinase C-terminal
iHog	**Q9VM64**	**DROME**	**swiss**	**886**	**100**	**100**	**Fibronectin type-III, Ig-like**
sax-3	O01632	CAEEL	trembl	1269	143/571 (25%)	212/571 (37%)	Fibronectin type-III, Ig-like
BOC	Q9BWV1	HUMAN	swiss	1114	160/624 (25%)	247/624 (39%)	Fibronectin type-III, Ig-like
Boc	Q6AZB0	MOUSE	swiss	1110	155/619 (25%)	241/619 (38%)	Fibronectin type-III, Ig-like
boc	Q90Z03	XENLA	trembl	1056	110/399 (27%)	167/399 (41%)	Fibronectin type-III, Ig-like
boc	Q8UVD6	DANRE	trembl	1032	129/510 (25%)	198/510 (38%)	Fibronectin type-III, Ig-like
boi	**Q8SX52**	**DROME**	**trembl**	**547**	**100**	**100**	**Fibronectin type-III, Ig-like**
sax-3	O01632	CAEEL	trembl	1269	143/571 (25%)	212/571 (37%)	Fibronectin type-III, Ig-like
CDO	Q4KMG0	HUMAN	swiss	1287	82/328 (25%)	143/328 (43%)	Fibronectin type-III, Ig-like
Cdo	Q32MD9	MOUSE	swiss	1250	84/328 (25%)	146/328 (44%)	Fibronectin type-III, Ig-like
cdo	Q90Z04	XENLA	swiss	1249	83/323 (25%)	144/323 (44%)	Fibronectin type-III, Ig-like
cdon	Q1L8D0	DANRE	trembl	1125	88/305 (28%)	137/305 (44%)	Fibronectin type-III, Ig-like
fu	**P23647**	**DROME**	**swiss**	**805**	**100**	**100**	**Protein kinase**
akt-1	Q17941	CAEEL	trembl	546	92/251 (36%)	139/251 (55%)	Protein kinase
STK36	Q9NRP7	HUMAN	swiss	1315	148/289 (51%)	202/289 (69%)	Protein kinase
Stk36	Q69ZM6	MOUSE	swiss	1268	119/224 (53%)	163/224 (72%)	Protein kinase
ulk3	Q4V7Q6	XENLA	swiss	468	99/263 (37%)	158/263 (60%)	Protein kinase
stk33	Q5RHZ0	DANRE	trembl	500	96/277 (34%)	155/277 (55%)	Protein kinase

Table A.2. Overall protein identity and conservation for Hedgehog signaling core proteins-continued

name	uni name	organism	source	aa length	identity %	conservation %	domains
Su(fu)	**Q9VG38**	**DROME**	**swiss**	**468**	**100**	**100**	**SUFU_domain**
		CAEEL	No significant similarity				
SUFU	Q9UMX1	HUMAN	swiss	484	177/464 (38%)	247/464 (53%)	SUFU_domain
Sufu	Q9Z0P7	MOUSE	swiss	484	173/458 (37%)	248/458 (54%)	SUFU_domain
sufu	Q6GN20	XENLA	trembl	474	178/464 (38%)	255/464 (54%)	SUFU_domain
sufu	Q7ZVZ9	DANRE	trembl	485	177/486 (36%)	258/486 (53%)	SUFU_domain
ci	**P19538**	**DROME**	**swiss**	**1397**	**100**	**100**	**ZINC_FINGER_C2H2**
tra-1	P34708	CAEEL	swiss	1110	108/175 (61%)	125/175 (71%)	ZINC_FINGER_C2H3
GLI2	P10070	HUMAN	swiss	1586	226/481 (46%)	276/481 (57%)	ZINC_FINGER_C2H2
Gli2	Q0VGV1	MOUSE	trembl	1540	227/496 (45%)	275/496 (55%)	ZINC_FINGER_C2H2
gli3	Q91660	XENLA	swiss	1569	300/783 (38%)	382/783 (48%)	ZINC_FINGER_C2H2
gli3	Q6U6Z9	DANRE	trembl	1553	198/409 (48%)	243/409 (59%)	ZINC_FINGER_C2H3

APPENDIX B: GO ANNOTATION COLLECTION TABLES

Table B.1. Cellular component terms of Wnt/β-catenin signaling pathway core proteins

GO ID	Cellular Component	GO ID	Cellular Component
5912	adherens junction	16021	integral to membrane
31225	anchored to membrane	5887	integral to plasma membrane
45179	apical cortex	5622	intracellular
45177	apical part of cell	5770	late endosome
16324	apical plasma membrane	5811	lipid particle
16327	apicolateral plasma membrane	16020	membrane
30424	axon	45121	membrane raft
16342	catenin complex	5875	microtubule associated complex
5938	cell cortex	152	nuclear ubiquitin ligase complex
9986	cell surface	5634	nucleus
5575	cellular_component unknown	5886	plasma membrane
32154	cleavage furrow	5578	proteinaceous extracellular matrix
5737	cytoplasm	19005	SCF ubiquitin ligase complex
16023	cytoplasmic membrane-bounded vesicle	5914	spot adherens junction
5769	early endosome	5667	transcription factor complex
5576	extracellular region	5669	transcription factor TFIID complex
19897	extrinsic to plasma membrane	151	ubiquitin ligase complex
5834	heterotrimeric G-protein complex	5915	zonula adherens
31011	Ino80 complex		

Table B.2. Molecular function terms of Wnt/β-catenin signaling pathway core proteins

GO ID	Molecular function	GO ID	Molecular function
8415	acyltransferase activity	5112	Notch binding
45294	alpha-catenin binding	8233	peptidase activity
5524	ATP binding	51219	phosphoprotein binding
8013	beta-catenin binding	5515	protein binding
5509	calcium ion binding	4672	protein kinase activity
8140	cAMP response element binding protein binding	4674	protein serine/threonine kinase activity
8092	cytoskeletal protein binding	4713	protein tyrosine kinase activity
3677	DNA binding	5102	receptor binding
3678	DNA helicase activity	3702	RNA polymerase II transcription factor activity
5110	frizzled-2 binding	4871	signal transducer activity
4696	glycogen synthase kinase 3 activity	16566	specific transcriptional repressor activity
4930	G-protein coupled receptor activity	5198	structural molecule activity
5525	GTP binding	16563	transcription activator activity
3924	GTPase activity	3713	transcription coactivator activity
4402	histone acetyltransferase activity (IEA)	3714	transcription corepressor activity
42802	identical protein binding	3700	transcription factor activity
8545	JUN kinase kinase kinase activity	8134	transcription factor binding
16301	kinase activity	30528	transcription regulator activity
5041	low-density lipoprotein receptor activity	5160	transforming growth factor beta receptor binding
287	magnesium ion binding	4888	transmembrane receptor activity
4707	MAP kinase activity	31625	ubiquitin protein ligase binding
8017	microtubule binding	4842	ubiquitin-protein ligase activity
3674	molecular function uknown	42813	Wnt receptor activity
16015	morphogen activity	17147	Wnt-protein binding
4926	non-G-protein coupled 7TM receptor activity	8270	zinc ion binding

Table B.3. Biological process terms of Wnt/β-catenin signaling pathway core proteins

GO ID	Biological Process	GO ID	Biological Process
7015	actin filament organization	7017	microtubule-based process
7256	activation of JNKK activity	7275	multicellular organismal development
35288	anterior head segmentation	16319	mushroom body development
35288	anterior head segmentation	9996	negative regulation of cell fate specification
6916	anti-apoptosis	46673	negative regulation of compound eye retinal cell programmed cell death
6915	apoptosis	45849	negative regulation of nurse cell apoptosis
8356	asymmetric cell division	45705	negative regulation of salivary gland boundary specification
8105	asymmetric protein localization	45879	negative regulation of smoothened signaling pathway
48675	axon extension	16481	negative regulation of transcription
7411	axon guidance	122	negative regulation of transcription from RNA polymerase II promoter
8150	biological process unknown	45892	negative regulation of transcription, DNA-dependent
7350	blastoderm segmentation	30512	negative regulation of transforming growth factor beta receptor signaling pathway
30509	BMP signaling pathway	30178	negative regulation of Wnt receptor signaling pathway
7298	border follicle cell migration	7399	nervous system development
35147	branch fusion, open tracheal system	14019	neuroblast development
8407	bristle morphogenesis	7400	neuroblast fate determination
10002	cardioblast differentiation	14018	neuroblast fate specification
7155	cell adhesion	7405	neuroblast proliferation
7049	cell cycle	48666	neuron development
51301	cell division	7269	neurotransmitter secretion
902	cell morphogenesis	7220	Notch receptor processing
48870	cell motility	7219	Notch signaling pathway
6928	cell motion	48802	notum morphogenesis
8283	cell proliferation	8355	olfactory learning
16337	cell-cell adhesion	16318	ommatidial rotation
8362	chitin-based embryonic cuticle biosynthetic process	30720	oocyte localization during germarium-derived egg chamber formation
35293	chitin-based larval cuticle pattern formation	48477	oogenesis
7304	chorion-containing eggshell formation	30707	ovarian follicle cell development
16568	chromatin modification	30713	ovarian follicle cell stalk formation
32922	circadian regulation of gene expression	7513	pericardial cell differentiation
7623	circadian rhythm	6911	phagocytosis, engulfment
48749	compound eye development	46530	photoreceptor cell differentiation
1745	compound eye morphogenesis	6963	positive regulation of antibacterial peptide biosynthetic process
46667	compound eye retinal cell programmed cell death	46672	positive regulation of compound eye retinal cell programmed cell death
30866	cortical actin cytoskeleton organization	10552	positive regulation of gene-specific transcription from RNA polymerase II promoter
35017	cuticle pattern formation	46330	positive regulation of JNK cascade
910	cytokinesis	45862	positive regulation of proteolysis

Table B.3. Biological process terms of Wnt/β-catenin signaling pathway core proteins-continued

GO ID	Biological Process	GO ID	Biological Process
7016	cytoskeletal anchoring at plasma membrane	45880	positive regulation of smoothened signaling pathway
7010	cytoskeletal organization and biogenesis	45887	positive regulation of synaptic growth at neuromuscular junction
7010	cytoskeleton organization	30177	positive regulation of Wnt receptor signaling pathway
8101	decapentaplegic receptor signaling pathway	35289	posterior head segmentation
48813	dendrite morphogenesis	48728	proboscis development
50908	detection of light stimulus involved in visual perception	10498	proteasomal protein catabolic process
8595	determination of anterior/posterior axis, embryo	6497	protein amino acid lipidation
35225	determination of genital disc primordium	18279	protein amino acid N-linked glycosylation via asparagine
6281	DNA repair	6468	protein amino acid phosphorylation
46843	dorsal appendage formation	30163	protein catabolic process
7391	dorsal closure	8104	protein localization
7394	dorsal closure, elongation of leading edge cells	18345	protein palmitoylation
9950	dorsal/ventral axis specification	9306	protein secretion
9953	dorsal/ventral pattern formation	50821	protein stabilization
9880	embryonic pattern specification	6622	protein targeting to lysosome
9649	entrainment of circadian clock	16567	protein ubiquitination
8544	epidermis development	6508	proteolysis
7425	epithelial cell fate determination, open tracheal system	7464	R3/R4 cell fate commitment
7163	establishment and/or maintenance of cell polarity	45466	R7 cell differentiation
60856	establishment of blood-brain barrier	7465	R7 cell fate commitment
48106	establishment of body bristle orientation	6898	receptor-mediated endocytosis
45198	establishment of epithelial cell apical/basal polarity	32231	regulation of actin filament bundle formation
1737	establishment of imaginal disc-derived wing hair orientation	51726	regulation of cell cycle
40001	establishment of mitotic spindle localization	42127	regulation of cell proliferation
42067	establishment of ommatidial polarity	8360	regulation of cell shape
1736	establishment of planar polarity	48076	regulation of compound eye pigmentation
7164	establishment of tissue polarity	45610	regulation of hemocyte differentiation
7163	establishment or maintenance of cell polarity	45570	regulation of imaginal disc growth
35214	eye-antennal disc development	7088	regulation of mitosis
7455	eye-antennal disc morphogenesis	7346	regulation of mitotic cell cycle
8585	female gonad development	40014	regulation of multicellular organism growth
46847	filopodium assembly	42306	regulation of protein import into nucleus
7440	foregut morphogenesis	30162	regulation of proteolysis
35224	genital disc anterior/posterior pattern formation	45676	regulation of R7 cell differentiation

Table B.3. Biological process terms of Wnt/β-catenin signaling pathway core proteins-continued

GO ID	Biological Process	GO ID	Biological Process
35263	genital disc sexually dimorphic development	8589	regulation of smoothened signaling pathway
7293	germarium-derived egg chamber formation	45449	regulation of transcription
30708	germarium-derived female germ-line cyst encapsulation	6357	regulation of transcription from RNA polymerase II promoter
30727	germarium-derived female germ-line cyst formation	6355	regulation of transcription, DNA-dependent
42078	germ-line stem cell division	30111	regulation of Wnt receptor signaling pathway
30718	germ-line stem cell maintenance	8588	release of cytoplasmic sequestered NF-kappaB
7186	G-protein coupled receptor protein signaling pathway	50896	response to stimulus
42332	gravitaxis	31290	retinal ganglion cell axon guidance
8258	head involution	7622	rhythmic behavior
7507	heart development	7435	salivary gland morphogenesis
30097	hemopoiesis	7367	segment polarity determination
7442	hindgut morphogenesis	8052	sensory organ boundary specification
7156	homophilic cell adhesion	7423	sensory organ development
7249	I-kappaB kinase/NF-kappaB cascade	16360	sensory organ precursor cell fate determination
7446	imaginal disc growth	19991	septate junction assembly
7447	imaginal disc pattern formation	7541	sex determination, primary response to X:A ratio
7480	imaginal disc-derived leg morphogenesis	7165	signal transduction
35317	imaginal disc-derived wing hair organization	7224	smoothened signaling pathway
35320	imaginal disc-derived wing hair site selection	35019	somatic stem cell maintenance
8587	imaginal disc-derived wing margin morphogenesis	35277	spiracle morphogenesis, open tracheal system
7476	imaginal disc-derived wing morphogenesis	51124	synaptic growth at neuromuscular junction
8586	imaginal disc-derived wing vein morphogenesis	35190	syncytial nuclear migration
7474	imaginal disc-derived wing vein specification	6351	transcription, DNA-dependent
6955	immune response	7179	transforming growth factor beta receptor signaling pathway
45087	innate immune response	35290	trunk segmentation
2168	instar larval development	6511	ubiquitin-dependent protein catabolic process
7242	intracellular signaling cascade	7419	ventral cord development
35217	labial disc development	7370	ventral furrow formation
30032	lamellipodium assembly	7418	ventral midline development
7523	larval visceral muscle development	7601	visual perception
7611	learning and/or memory	35309	wing and notum subfield formation
7479	leg disc proximal/distal pattern formation	35311	wing cell fate specification
45475	locomotor rhythm	48100	wing disc anterior/posterior pattern formation
48542	lymph gland development	48190	wing disc dorsal/ventral pattern formation
21550	medulla oblongata development	7473	wing disc proximal/distal pattern formation
8315	meiotic G2/MI transition	16055	Wnt receptor signaling pathway

Table B.3. Biological process terms of Wnt/β-catenin signaling pathway core proteins-continued

GO ID	Biological Process	GO ID	Biological Process
6509	membrane protein ectodomain proteolysis	7223	Wnt receptor signaling pathway, calcium modulating pathway
48332	mesoderm morphogenesis	60071	Wnt receptor signaling pathway, planar cell polarity pathway
7500	mesodermal cell fate determination	45186	zonula adherens assembly

Table B.4. Cellular component terms of Hedgehog signaling pathway core proteins

GO ID	Cellular Component
9986	cell surface
5575	cellular_component unknown
31461	cullin-RING ubiquitin ligase complex
5737	cytoplasm
16023	cytoplasmic membrane-bounded vesicle
30139	endocytic vesicle
5783	endoplasmic reticulum
5768	endosome
5576	extracellular region
19897	extrinsic to plasma membrane
45169	fusome
5794	Golgi apparatus
35301	Hedgehog signaling complex
16021	integral to membrane
16021	integral to membrane
5887	integral to plasma membrane
31227	intrinsic to endoplasmic reticulum membrane
5871	kinesin complex
5811	lipid particle
16020	membrane
16020	membrane
5875	microtubule associated complex
152	nuclear ubiquitin ligase complex
5634	nucleus
48471	perinuclear region of cytoplasm
5886	plasma membrane
5578	proteinaceous extracellular matrix
19005	SCF ubiquitin ligase complex
151	ubiquitin ligase complex
12506	vesicle membrane

Table B.5. Molecular function terms of Hedgehog signaling pathway core proteins

GO ID	Molecular function	GO ID	Molecular function
8375	acetylglucosaminyltransferase activity	4926	non-G-protein coupled 7TM receptor activity
8415	acyltransferase activity	3676	nucleic acid binding
5524	ATP binding	16409	palmitoyltransferase activity
4691	cAMP-dependent protein kinase activity	5113	patched binding
43498	cell surface binding	8233	peptidase activity
4197	cysteine-type endopeptidase activity	51219	phosphoprotein binding
4175	endopeptidase activity	5515	protein binding
5504	fatty acid binding	42803	protein homodimerization activity
50508	glucuronosyl-N-acetylglucosaminyl-proteoglycan 4-alpha-N-acetylglucosaminyltransferase activity	4672	protein kinase activity
15020	glucuronosyltransferase activity	19901	protein kinase binding
4696	glycogen synthase kinase 3 activity	4674	protein serine/threonine kinase activity
4930	G-protein coupled receptor activity	4713	protein tyrosine kinase activity
4703	G-protein coupled receptor kinase activity	5102	receptor binding
8158	hedgehog receptor activity	5501	retinoid binding
20037	heme binding	19841	retinol binding
43395	heparan sulfate proteoglycan binding	4871	signal transducer activity
8201	heparin binding	5119	smoothened binding
16301	kinase activity	3704	specific RNA polymerase II transcription factor activity
5319	lipid transporter activity	5198	structural molecule activity
30228	lipoprotein receptor activity	16563	transcription activator activity
8017	microtubule binding	3700	transcription factor activity
3777	microtubule motor activity	16564	transcription repressor activity
3674	molecular function uknown	4888	transmembrane receptor activity
16015	morphogen activity	31625	ubiquitin protein ligase binding
3774	motor activity	4842	ubiquitin-protein ligase activity
50509	N-acetylglucosaminyl-proteoglycan 4-beta-glucuronosyltransferase activity	8270	zinc ion binding

Table B.6. Biological process terms of Hedgehog signaling pathway core proteins

GO ID	Biological Process	GO ID	Biological Process
7487	analia development	45749	negative regulation of S phase of mitotic cell cycle
21960	anterior commissure morphogenesis	45879	negative regulation of smoothened signaling pathway
35288	anterior head segmentation	42992	negative regulation of transcription factor import into nucleus
48099	anterior/posterior lineage restriction, imaginal disc	122	negative regulation of transcription from RNA polymerase II promoter
9952	anterior/posterior pattern formation	30512	negative regulation of transforming growth factor beta receptor signaling pathway
7448	anterior/posterior pattern formation, imaginal disc	30178	negative regulation of Wnt receptor signaling pathway
7411	axon guidance	7399	nervous system development
7409	axonogenesis	48666	neuron development
48149	behavioral response to ethanol	7219	Notch signaling pathway
8150	biological process unknown	18009	N-terminal peptidyl-L-cysteine N-palmitoylation
7350	blastoderm segmentation	8355	olfactory learning
1746	Bolwig's organ morphogenesis	7314	oocyte anterior/posterior axis specification
7298	border follicle cell migration	30720	oocyte localization during germarium-derived egg chamber formation
22416	bristle development	8103	oocyte microtubule cytoskeleton polarization
8407	bristle morphogenesis	48477	oogenesis
5952	cAMP-dependent protein kinase complex	7424	open tracheal system development
19933	cAMP-mediated signaling	30707	ovarian follicle cell development
7155	cell adhesion	30713	ovarian follicle cell stalk formation
8283	cell proliferation	7225	patched ligand processing
7267	cell-cell signaling	7422	peripheral nervous system development
7304	chorion-containing eggshell formation	6911	phagocytosis, engulfment
7623	circadian rhythm	48066	pigmentation during development
7386	compartment specification	7280	pole cell migration
48749	compound eye development	7228	positive regulation of hh target transcription factor activity
1745	compound eye morphogenesis	45750	positive regulation of S phase of mitotic cell cycle
1751	compound eye photoreceptor cell differentiation	45880	positive regulation of smoothened signaling pathway
35017	cuticle pattern formation	45944	positive regulation of transcription from RNA polymerase II promoter
35231	cytoneme assembly	35289	posterior head segmentation
8101	decapentaplegic receptor signaling pathway	7458	progression of morphogenetic furrow during compound eye morphogenesis
48813	dendrite morphogenesis	18318	protein amino acid palmitoylation
16311	dephosphorylation	6468	protein amino acid phosphorylation
50908	detection of light stimulus involved in visual perception	16540	protein autoprocessing

Table B.6. Biological process terms of Hedgehog signaling pathway core proteins-continued

GO ID	Biological Process	GO ID	Biological Process
8595	determination of anterior/posterior axis, embryo	30163	protein catabolic process
35225	determination of genital disc primordium	6606	protein import into nucleus
6281	DNA repair	8104	protein localization
46843	dorsal appendage formation	18345	protein palmitoylation
7398	ectoderm development	30908	protein splicing
9880	embryonic pattern specification	50821	protein stabilization
9649	entrainment of circadian clock	16567	protein ubiquitination
8544	epidermis development	42787	protein ubiquitination during ubiquitin-dependent protein catabolic process
7427	epithelial cell migration, open tracheal system	6508	proteolysis
6887	exocytosis	45464	R8 cell fate specification
48592	eye morphogenesis	8359	regulation of bicoid mRNA localization
7455	eye-antennal disc morphogenesis	51726	regulation of cell cycle
7440	foregut morphogenesis	42127	regulation of cell proliferation
35224	genital disc anterior/posterior pattern formation	42752	regulation of circadian rhythm
35215	genital disc development	45187	regulation of circadian sleep/wake cycle, sleep
35232	germ cell attraction	8277	regulation of G-protein coupled receptor protein signaling pathway
8354	germ cell migration	45610	regulation of hemocyte differentiation
7293	germarium-derived egg chamber formation	45570	regulation of imaginal disc growth
30708	germarium-derived female germ-line cyst encapsulation	7088	regulation of mitosis
30727	germarium-derived female germ-line cyst formation	7346	regulation of mitotic cell cycle
42078	germ-line stem cell division	40014	regulation of multicellular organism growth
8347	glial cell migration	46620	regulation of organ growth
6024	glycosaminoglycan biosynthetic process	7317	regulation of pole plasm oskar mRNA localization
7506	gonadal mesoderm development	42306	regulation of protein import into nucleus
7186	G-protein coupled receptor protein signaling pathway	31647	regulation of protein stability
40007	growth	30162	regulation of proteolysis
46959	habituation	8589	regulation of smoothened signaling pathway
7507	heart development	45449	regulation of transcription
15012	heparan sulfate proteoglycan biosynthetic process	6357	regulation of transcription from RNA polymerase II promoter
15014	heparan sulfate proteoglycan biosynthetic process, polysaccharide chain biosynthetic process	6355	regulation of transcription, DNA-dependent

Table B.6. Biological process terms of Hedgehog signaling pathway core proteins-continued

GO ID	Biological Process	GO ID	Biological Process
30210	heparin biosynthetic process	30111	regulation of Wnt receptor signaling pathway
7442	hindgut morphogenesis	8588	release of cytoplasmic sequestered NF-kappaB
7446	imaginal disc growth	7622	rhythmic behavior
7447	imaginal disc pattern formation	7367	segment polarity determination
7480	imaginal disc-derived leg morphogenesis	8052	sensory organ boundary specification
8587	imaginal disc-derived wing margin morphogenesis	7423	sensory organ development
7476	imaginal disc-derived wing morphogenesis	7165	signal transduction
8586	imaginal disc-derived wing vein morphogenesis	7224	smoothened signaling pathway
7474	imaginal disc-derived wing vein specification	7224	smoothened signaling pathway
16539	intein-mediated protein splicing	48103	somatic stem cell division
2121	inter-male aggressive behavior	35019	somatic stem cell maintenance
35217	labial disc development	35277	spiracle morphogenesis, open tracheal system
7612	learning	51124	synaptic growth at neuromuscular junction
7611	learning or memory	7179	transforming growth factor beta receptor signaling pathway
7478	leg disc morphogenesis	6810	transport
55088	lipid homeostasis	35290	trunk segmentation
6869	lipid transport	6511	ubiquitin-dependent protein catabolic process
45475	locomotor rhythm	7418	ventral midline development
8315	meiotic G2/MI transition	35309	wing and notum subfield formation
7613	memory	48100	wing disc anterior/posterior pattern formation
7498	mesoderm development	35220	wing disc development
7018	microtubule-based movement	48190	wing disc dorsal/ventral pattern formation
16335	morphogenesis of larval imaginal disc epithelium	7472	wing disc morphogenesis
6044	N-acetylglucosamine metabolic process	35222	wing disc pattern formation
45849	negative regulation of nurse cell apoptosis	7473	wing disc proximal/distal pattern formation
42308	negative regulation of protein import into nucleus	16055	Wnt receptor signaling pathway
45861	negative regulation of proteolysis		

APPENDIX C: PROTEIN INTERACTIONS IN THE RECONSTRUCTED NETWORKS IN *D. MELANOGASTER*

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in D. melanogaster

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0003124	FBgn0000179	FBgn0003870	FBgn0026262	FBgn0002781	FBgn0026369
FBgn0001168	FBgn0003944	FBgn0003944	FBgn0005596	FBgn0002609	FBgn0002609
FBgn0040080	FBgn0001122	FBgn0000258	FBgn0260934	FBgn0027066	FBgn0259794
FBgn0039044	FBgn0035357	FBgn0000233	FBgn0010280	FBgn0010315	FBgn0085432
FBgn0028734	FBgn0003896	FBgn0003410	FBgn0013765	FBgn0004858	FBgn0038852
FBgn0028902	FBgn0036274	FBgn0028577	FBgn0038271	FBgn0004859	FBgn0001078
FBgn0031537	FBgn0250788	FBgn0019686	FBgn0023091	FBgn0011661	FBgn0011661
FBgn0025743	FBgn0086364	FBgn0000117	FBgn0010215	FBgn0051999	FBgn0022382
FBgn0000413	FBgn0002633	FBgn0003944	FBgn0025800	FBgn0015805	FBgn0027950
FBgn0000413	FBgn0002631	FBgn0000588	FBgn0015805	FBgn0004859	FBgn0013759
FBgn0020496	FBgn0023444	FBgn0004859	FBgn0053519	FBgn0003118	FBgn0023214
FBgn0086358	FBgn0038271	FBgn0020503	FBgn0021760	FBgn0001139	FBgn0001168
FBgn0024371	FBgn0000166	FBgn0001139	FBgn0002633	FBgn0001120	FBgn0000338
FBgn0004859	FBgn0038271	FBgn0003892	FBgn0042630	FBgn0023423	FBgn0026175
FBgn0015331	FBgn0033029	FBgn0039044	FBgn0023091	FBgn0014143	FBgn0039286
FBgn0000721	FBgn0005630	FBgn0037734	FBgn0003941	FBgn0000137	FBgn0000575
FBgn0025637	FBgn0000166	FBgn0004895	FBgn0004870	FBgn0038576	FBgn0003495
FBgn0023522	FBgn0000996	FBgn0011661	FBgn0013984	FBgn0011661	FBgn0001075
FBgn0001168	FBgn0001168	FBgn0008646	FBgn0011640	FBgn0004859	FBgn0039283
FBgn0000182	FBgn0004882	FBgn0003892	FBgn0003328	FBgn0015282	FBgn0000229
FBgn0027574	FBgn0020386	FBgn0003371	FBgn0015589	FBgn0003892	FBgn0035357
FBgn0001323	FBgn0001624	FBgn0037555	FBgn0053520	FBgn0000259	FBgn0011277
FBgn0001324	FBgn0015618	FBgn0003892	FBgn0053208	FBgn0013263	FBgn0002781
FBgn0011661	FBgn0034400	FBgn0019650	FBgn0003345	FBgn0000273	FBgn0003429
FBgn0013725	FBgn0001233	FBgn0036661	FBgn0000253	FBgn0020369	FBgn0035849
FBgn0025743	FBgn0003479	FBgn0037555	FBgn0037981	FBgn0032475	FBgn0035976
FBgn0025806	FBgn0086364	FBgn0003943	FBgn0031450	FBgn0051999	FBgn0000319
FBgn0004106	FBgn0010315	FBgn0000629	FBgn0000629	FBgn0004859	FBgn0086902
FBgn0039044	FBgn0000166	FBgn0000504	FBgn0037811	FBgn0000251	FBgn0000258
FBgn0001133	FBgn0001133	FBgn0026318	FBgn0026318	FBgn0011300	FBgn0053967
FBgn0019650	FBgn0001219	FBgn0010379	FBgn0001148	FBgn0000413	FBgn0000591
FBgn0020255	FBgn0041582	FBgn0001079	FBgn0000028	FBgn0036697	FBgn0001320
FBgn0000229	FBgn0003464	FBgn0003479	FBgn0033636	FBgn0023388	FBgn0004598
FBgn0011648	FBgn0011655	FBgn0003944	FBgn0013591	FBgn0013765	FBgn0000273
FBgn0002973	FBgn0015567	FBgn0004859	FBgn0003425	FBgn0000617	FBgn0011290
FBgn0011715	FBgn0003345	FBgn0038747	FBgn0003464	FBgn0000212	FBgn0040078
FBgn0026318	FBgn0030941	FBgn0015286	FBgn0052532	FBgn0005630	FBgn0005630
FBgn0004870	FBgn0250785	FBgn0031850	FBgn0259481	FBgn0015790	FBgn0032105
FBgn0010342	FBgn0010342	FBgn0042630	FBgn0003942	FBgn0013263	FBgn0026262
FBgn0001319	FBgn0003345	FBgn0010315	FBgn0008646	FBgn0035993	FBgn0004606
FBgn0003687	FBgn0037555	FBgn0031450	FBgn0250788	FBgn0028642	FBgn0013718
FBgn0000042	FBgn0000212	FBgn0010333	FBgn0025740	FBgn0030242	FBgn0039946
FBgn0000166	FBgn0000439	FBgn0001323	FBgn0001122	FBgn0003068	FBgn0023423
FBgn0026411	FBgn0003464	FBgn0002734	FBgn0002734	FBgn0031450	FBgn0020496
FBgn0001981	FBgn0020496	FBgn0002734	FBgn0002735	FBgn0013753	FBgn0013755

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in *D. melanogaster*-continued

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0003870	FBgn0259794	FBgn0013531	FBgn0038578	FBgn0001150	FBgn0040078
FBgn0003254	FBgn0022238	FBgn0015624	FBgn0023091	FBgn0026192	FBgn0243505
FBgn0041582	FBgn0000611	FBgn0086384	FBgn0015371	FBgn0002121	FBgn0022131
FBgn0010379	FBgn0042630	FBgn0038035	FBgn0053208	FBgn0051999	FBgn0000578
FBgn0024184	FBgn0001139	FBgn0003002	FBgn0003464	FBgn0004859	FBgn0001235
FBgn0002609	FBgn0010433	FBgn0086358	FBgn0002985	FBgn0003124	FBgn0015550
FBgn0000166	FBgn0015602	FBgn0000042	FBgn0011771	FBgn0015331	FBgn0000338
FBgn0001170	FBgn0002940	FBgn0028642	FBgn0026597	FBgn0031850	FBgn0001981
FBgn0041171	FBgn0025741	FBgn0004837	FBgn0011290	FBgn0260632	FBgn0000504
FBgn0000229	FBgn0003475	FBgn0010109	FBgn0010109	FBgn0001624	FBgn0003380
FBgn0000499	FBgn0005558	FBgn0259220	FBgn0023091	FBgn0037466	FBgn0259794
FBgn0086384	FBgn0039283	FBgn0000166	FBgn0004893	FBgn0000625	FBgn0250789
FBgn0024371	FBgn0000578	FBgn0003124	FBgn0004394	FBgn0041171	FBgn0011260
FBgn0004896	FBgn0000524	FBgn0027609	FBgn0025637	FBgn0086384	FBgn0011661
FBgn0031537	FBgn0020379	FBgn0003129	FBgn0026170	FBgn0031450	FBgn0001235
FBgn0011661	FBgn0051619	FBgn0000212	FBgn0087008	FBgn0040080	FBgn0040080
FBgn0027788	FBgn0034160	FBgn0003013	FBgn0011715	FBgn0000463	FBgn0039283
FBgn0003720	FBgn0020496	FBgn0011648	FBgn0000166	FBgn0004896	FBgn0039066
FBgn0061173	FBgn0026313	FBgn0067864	FBgn0259685	FBgn0026263	FBgn0026262
FBgn0029711	FBgn0051619	FBgn0053967	FBgn0086358	FBgn0019650	FBgn0000448
FBgn0008651	FBgn0036274	FBgn0032956	FBgn0085432	FBgn0013765	FBgn0000250
FBgn0250785	FBgn0038046	FBgn0250785	FBgn0033483	FBgn0025806	FBgn0023172
FBgn0028577	FBgn0013725	FBgn0003460	FBgn0023172	FBgn0051999	FBgn0024250
FBgn0028734	FBgn0028734	FBgn0011661	FBgn0036254	FBgn0023215	FBgn0029114
FBgn0000166	FBgn0033073	FBgn0003892	FBgn0030600	FBgn0000117	FBgn0085432
FBgn0004647	FBgn0000179	FBgn0003892	FBgn0000546	FBgn0003448	FBgn0020496
FBgn0004647	FBgn0038578	FBgn0050011	FBgn0024491	FBgn0024732	FBgn0038341
FBgn0011276	FBgn0000413	FBgn0003429	FBgn0024728	FBgn0086384	FBgn0004049
FBgn0015024	FBgn0015589	FBgn0004603	FBgn0000524	FBgn0004859	FBgn0004607
FBgn0000560	FBgn0020496	FBgn0031850	FBgn0003031	FBgn0003600	FBgn0015805
FBgn0038852	FBgn0000182	FBgn0000046	FBgn0040080	FBgn0029711	FBgn0038341
FBgn0015286	FBgn0010194	FBgn0004859	FBgn0028789	FBgn0011648	FBgn0041582
FBgn0003410	FBgn0003410	FBgn0001085	FBgn0024836	FBgn0003892	FBgn0259217
FBgn0000499	FBgn0004647	FBgn0001168	FBgn0002609	FBgn0011661	FBgn0004583
FBgn0023509	FBgn0038390	FBgn0011586	FBgn0000524	FBgn0025806	FBgn0005558
FBgn0038035	FBgn0033636	FBgn0005771	FBgn0040918	FBgn0004647	FBgn0085445
FBgn0005558	FBgn0003607	FBgn0033998	FBgn0015602	FBgn0036497	FBgn0041582
FBgn0002121	FBgn0026192	FBgn0000022	FBgn0002609	FBgn0003448	FBgn0023444
FBgn0008651	FBgn0001139	FBgn0025637	FBgn0035975	FBgn0003892	FBgn0003896
FBgn0015014	FBgn0015542	FBgn0027356	FBgn0027356	FBgn0000258	FBgn0002633
FBgn0011648	FBgn0002973	FBgn0022959	FBgn0011290	FBgn0004510	FBgn0000472
FBgn0002631	FBgn0001139	FBgn0039585	FBgn0032515	FBgn0003892	FBgn0003892
FBgn0011661	FBgn0003942	FBgn0003460	FBgn0004863	FBgn0003334	FBgn0003334
FBgn0003430	FBgn0001139	FBgn0031450	FBgn0023172	FBgn0001269	FBgn0086910
FBgn0004666	FBgn0015014	FBgn0003256	FBgn0003256	FBgn0011661	FBgn0086758
FBgn0035849	FBgn0011715	FBgn0031850	FBgn0015778	FBgn0000382	FBgn0004907
FBgn0004859	FBgn0031537	FBgn0053520	FBgn0004863	FBgn0020496	FBgn0024250
FBgn0024371	FBgn0016081	FBgn0013263	FBgn0024491	FBgn0011737	FBgn0030695
FBgn0041582	FBgn0053980	FBgn0024371	FBgn0025334	FBgn0003944	FBgn0022720
FBgn0004914	FBgn0015542	FBgn0003300	FBgn0013755	FBgn0000463	FBgn0029687
FBgn0001319	FBgn0000606	FBgn0000577	FBgn0022720	FBgn0000635	FBgn0026313
FBgn0000330	FBgn0024728	FBgn0011648	FBgn0085432	FBgn0085410	FBgn0000042
FBgn0011274	FBgn0038578	FBgn0003300	FBgn0013753	FBgn0001120	FBgn0024250
FBgn0003495	FBgn0003717	FBgn0039788	FBgn0039509	FBgn0000137	FBgn0002633

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in *D. melanogaster*-continued

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0033015	FBgn0011277	FBgn0024330	FBgn0030749	FBgn0003430	FBgn0038271
FBgn0003479	FBgn0003479	FBgn0004859	FBgn0259785	FBgn0003345	FBgn0028999
FBgn0003892	FBgn0053519	FBgn0260632	FBgn0035989	FBgn0001122	FBgn0014010
FBgn0015799	FBgn0024371	FBgn0000017	FBgn0000578	FBgn0011648	FBgn0053936
FBgn0015371	FBgn0001233	FBgn0038046	FBgn0017453	FBgn0004859	FBgn0001320
FBgn0000463	FBgn0085451	FBgn0010215	FBgn0015609	FBgn0004647	FBgn0085451
FBgn0031450	FBgn0001324	FBgn0000166	FBgn0036274	FBgn0026597	FBgn0000499
FBgn0041171	FBgn0002921	FBgn0020381	FBgn0038928	FBgn0004510	FBgn0260934
FBgn0008651	FBgn0003464	FBgn0022131	FBgn0026192	FBgn0035993	FBgn0035993
FBgn0010323	FBgn0039936	FBgn0000964	FBgn0016797	FBgn0001291	FBgn0026262
FBgn0024371	FBgn0015904	FBgn0015903	FBgn0026262	FBgn0004009	FBgn0001085
FBgn0003124	FBgn0016977	FBgn0003892	FBgn0259174	FBgn0004644	FBgn0031872
FBgn0024371	FBgn0000546	FBgn0004837	FBgn0001169	FBgn0000617	FBgn0037981
FBgn0041582	FBgn0001990	FBgn0002735	FBgn0004170	FBgn0001319	FBgn0033636
FBgn0015624	FBgn0008646	FBgn0052486	FBgn0052486	FBgn0011661	FBgn0087008
FBgn0003511	FBgn0250785	FBgn0031537	FBgn0030600	FBgn0001139	FBgn0002735
FBgn0028902	FBgn0001942	FBgn0031850	FBgn0003053	FBgn0001139	FBgn0002733
FBgn0003892	FBgn0011300	FBgn0001978	FBgn0028852	FBgn0000964	FBgn0002985
FBgn0004647	FBgn0036558	FBgn0000575	FBgn0011277	FBgn0086384	FBgn0010452
FBgn0011661	FBgn0004606	FBgn0005630	FBgn0015903	FBgn0019650	FBgn0003651
FBgn0000259	FBgn0000524	FBgn0086384	FBgn0003567	FBgn0020496	FBgn0039283
FBgn0015778	FBgn0259794	FBgn0000117	FBgn0039907	FBgn0015624	FBgn0000578
FBgn0050011	FBgn0050011	FBgn0000108	FBgn0000635	FBgn0001202	FBgn0011277
FBgn0003425	FBgn0005631	FBgn0028642	FBgn0002521	FBgn0002914	FBgn0023509
FBgn0000283	FBgn0035769	FBgn0013765	FBgn0022720	FBgn0000413	FBgn0000413
FBgn0004859	FBgn0002413	FBgn0003900	FBgn0260632	FBgn0032956	FBgn0038035
FBgn0001079	FBgn0000352	FBgn0027788	FBgn0011481	FBgn0000629	FBgn0001219
FBgn0028734	FBgn0000250	FBgn0041582	FBgn0000504	FBgn0003687	FBgn0053520
FBgn0003460	FBgn0001139	FBgn0001079	FBgn0010110	FBgn0000028	FBgn0086680
FBgn0086384	FBgn0023215	FBgn0015903	FBgn0015903	FBgn0022238	FBgn0011236
FBgn0086358	FBgn0260635	FBgn0011648	FBgn0035150	FBgn0019650	FBgn0000490
FBgn0026597	FBgn0003371	FBgn0002781	FBgn0026170	FBgn0011715	FBgn0005631
FBgn0003410	FBgn0050420	FBgn0086384	FBgn0086758	FBgn0259785	FBgn0259794
FBgn0003892	FBgn0016797	FBgn0025800	FBgn0004053	FBgn0002781	FBgn0003567
FBgn0000499	FBgn0053208	FBgn0002023	FBgn0024321	FBgn0002631	FBgn0002631
FBgn0016977	FBgn0037093	FBgn0026562	FBgn0011737	FBgn0000253	FBgn0000140
FBgn0010825	FBgn0015805	FBgn0002633	FBgn0010433	FBgn0002631	FBgn0002633
FBgn0086358	FBgn0004595	FBgn0026411	FBgn0000259	FBgn0025637	FBgn0001965
FBgn0085369	FBgn0001990	FBgn0000330	FBgn0010417	FBgn0000212	FBgn0001219
FBgn0003944	FBgn0011817	FBgn0000575	FBgn0004170	FBgn0015589	FBgn0003410
FBgn0002633	FBgn0004170	FBgn0000352	FBgn0003444	FBgn0001170	FBgn0032515
FBgn0010341	FBgn0026192	FBgn0259794	FBgn0039936	FBgn0003892	FBgn0004915
FBgn0003129	FBgn0011577	FBgn0011648	FBgn0004053	FBgn0001170	FBgn0011715
FBgn0001324	FBgn0003415	FBgn0003892	FBgn0003502	FBgn0038747	FBgn0002985
FBgn0001078	FBgn0028386	FBgn0004907	FBgn0028902	FBgn0013531	FBgn0024330
FBgn0030899	FBgn0001139	FBgn0015286	FBgn0085445	FBgn0003124	FBgn0086758
FBgn0027052	FBgn0001219	FBgn0019650	FBgn0003567	FBgn0020381	FBgn0086902
FBgn0001291	FBgn0028550	FBgn0000330	FBgn0029711	FBgn0001323	FBgn0020496
FBgn0000166	FBgn0031850	FBgn0003410	FBgn0003382	FBgn0086384	FBgn0003870
FBgn0004907	FBgn0259794	FBgn0010825	FBgn0040372	FBgn0013750	FBgn0032872
FBgn0015602	FBgn0015602	FBgn0001079	FBgn0040080	FBgn0002734	FBgn0001139
FBgn0035993	FBgn0029687	FBgn0003124	FBgn0002922	FBgn0038035	FBgn0035357
FBgn0028734	FBgn0036274	FBgn0015509	FBgn0025637	FBgn0002733	FBgn0002733
FBgn0003749	FBgn0015014	FBgn0015509	FBgn0025638	FBgn0001120	FBgn0001085

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in *D. melanogaster*-continued

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0086384	FBgn0002780	FBgn0019809	FBgn0052280	FBgn0002733	FBgn0002734
FBgn0011715	FBgn0011225	FBgn0000588	FBgn0024491	FBgn0002733	FBgn0002735
FBgn0028926	FBgn0011291	FBgn0001170	FBgn0024234	FBgn0011715	FBgn0026208
FBgn0003044	FBgn0010194	FBgn0028408	FBgn0028407	FBgn0000119	FBgn0016797
FBgn0022382	FBgn0011586	FBgn0259220	FBgn0004878	FBgn0010323	FBgn0086711
FBgn0000042	FBgn0040078	FBgn0039044	FBgn0035849	FBgn0011763	FBgn0023509
FBgn0004859	FBgn0040080	FBgn0000964	FBgn0003464	FBgn0000137	FBgn0002733
FBgn0040466	FBgn0260632	FBgn0004915	FBgn0010287	FBgn0053531	FBgn0026262
FBgn0010379	FBgn0259217	FBgn0000114	FBgn0000392	FBgn0000137	FBgn0002735
FBgn0041582	FBgn0000042	FBgn0003464	FBgn0024250	FBgn0005771	FBgn0005771
FBgn0004510	FBgn0052343	FBgn0004859	FBgn0000114	FBgn0001981	FBgn0000524
FBgn0020369	FBgn0036224	FBgn0011648	FBgn0029006	FBgn0260632	FBgn0020496
FBgn0086384	FBgn0010355	FBgn0031537	FBgn0039283	FBgn0003892	FBgn0003479
FBgn0002914	FBgn0015799	FBgn0037981	FBgn0053520	FBgn0013750	FBgn0087002
FBgn0011661	FBgn0039209	FBgn0025458	FBgn0029708	FBgn0086384	FBgn0010434
FBgn0013718	FBgn0003464	FBgn0003124	FBgn0039601	FBgn0028642	FBgn0259794
FBgn0003870	FBgn0000008	FBgn0028734	FBgn0027052	FBgn0000258	FBgn0002631
FBgn0039585	FBgn0001942	FBgn0004859	FBgn0002922	FBgn0003013	FBgn0004050
FBgn0001269	FBgn0001139	FBgn0035638	FBgn0001148	FBgn0031878	FBgn0000140
FBgn0003944	FBgn0005771	FBgn0039788	FBgn0026056	FBgn0001319	FBgn0042650
FBgn0002633	FBgn0002734	FBgn0010109	FBgn0001139	FBgn0086384	FBgn0003448
FBgn0002633	FBgn0002733	FBgn0040080	FBgn0004856	FBgn0011674	FBgn0026319
FBgn0001219	FBgn0003044	FBgn0004896	FBgn0021760	FBgn0025800	FBgn0011277
FBgn0039946	FBgn0011260	FBgn0002873	FBgn0040080	FBgn0000251	FBgn0005771
FBgn0002633	FBgn0002735	FBgn0000283	FBgn0002781	FBgn0000591	FBgn0002735
FBgn0086384	FBgn0010349	FBgn0003002	FBgn0044323	FBgn0000591	FBgn0002734
FBgn0027788	FBgn0004861	FBgn0000414	FBgn0004638	FBgn0026597	FBgn0000117
FBgn0005355	FBgn0039936	FBgn0001319	FBgn0003053	FBgn0000591	FBgn0002733
FBgn0019650	FBgn0004364	FBgn0003044	FBgn0020887	FBgn0000258	FBgn0000591
FBgn0004859	FBgn0020379	FBgn0028577	FBgn0003942	FBgn0010323	FBgn0000529
FBgn0011648	FBgn0039286	FBgn0000250	FBgn0000250	FBgn0003861	FBgn0004435
FBgn0000529	FBgn0020224	FBgn0000022	FBgn0002633	FBgn0001965	FBgn0004638
FBgn0003460	FBgn0046874	FBgn0026562	FBgn0003464	FBgn0003892	FBgn0003448
FBgn0085369	FBgn0086384	FBgn0003986	FBgn0024245	FBgn0000046	FBgn0015550
FBgn0013765	FBgn0002914	FBgn0000382	FBgn0003366	FBgn0026611	FBgn0039016
FBgn0040080	FBgn0026192	FBgn0259794	FBgn0000289	FBgn0001291	FBgn0003124
FBgn0260632	FBgn0004638	FBgn0039044	FBgn0026262	FBgn0000964	FBgn0002932
FBgn0039585	FBgn0015542	FBgn0002932	FBgn0004197	FBgn0000042	FBgn0003013
FBgn0004859	FBgn0030018	FBgn0020369	FBgn0013765	FBgn0023215	FBgn0021760
FBgn0031851	FBgn0001990	FBgn0028685	FBgn0036224	FBgn0010333	FBgn0026192
FBgn0036134	FBgn0259794	FBgn0013983	FBgn0036697	FBgn0001139	FBgn0003300
FBgn0038747	FBgn0032202	FBgn0001079	FBgn0004859	FBgn0003345	FBgn0003975
FBgn0086358	FBgn0259794	FBgn0000330	FBgn0036224	FBgn0017578	FBgn0000472
FBgn0003410	FBgn0023444	FBgn0004859	FBgn0000319	FBgn0010280	FBgn0013263
FBgn0024371	FBgn0004863	FBgn0002940	FBgn0003861	FBgn0086384	FBgn0035357
FBgn0000996	FBgn0033081	FBgn0003892	FBgn0011661	FBgn0003371	FBgn0025680
FBgn0025743	FBgn0000157	FBgn0004859	FBgn0027343	FBgn0035954	FBgn0002023
FBgn0020369	FBgn0002985	FBgn0003717	FBgn0003717	FBgn0024371	FBgn0041094
FBgn0001219	FBgn0003944	FBgn0024371	FBgn0259217	FBgn0026170	FBgn0260632
FBgn0001170	FBgn0004649	FBgn0086384	FBgn0015509	FBgn0017453	FBgn0000042
FBgn0004858	FBgn0003002	FBgn0040078	FBgn0000117	FBgn0020369	FBgn0028685
FBgn0000413	FBgn0010109	FBgn0004652	FBgn0051999	FBgn0000577	FBgn0003464
FBgn0015371	FBgn0026262	FBgn0004907	FBgn0003464	FBgn0001291	FBgn0001297
FBgn0025637	FBgn0011586	FBgn0038928	FBgn0013983	FBgn0004870	FBgn0011715

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in *D. melanogaster*-continued

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0005631	FBgn0005631	FBgn0086384	FBgn0053967	FBgn0020369	FBgn0028687
FBgn0000591	FBgn0001168	FBgn0086384	FBgn0032467	FBgn0030318	FBgn0002940
FBgn0000524	FBgn0004647	FBgn0005771	FBgn0000042	FBgn0031450	FBgn0000250
FBgn0024846	FBgn0003511	FBgn0037937	FBgn0000413	FBgn0026056	FBgn0015542
FBgn0000504	FBgn0046874	FBgn0029711	FBgn0001090	FBgn0001079	FBgn0003444
FBgn0000463	FBgn0010355	FBgn0000259	FBgn0008649	FBgn0001291	FBgn0001291
FBgn0000560	FBgn0002733	FBgn0015282	FBgn0028687	FBgn0032515	FBgn0039016
FBgn0028902	FBgn0001981	FBgn0035849	FBgn0015542	FBgn0032515	FBgn0032515
FBgn0013718	FBgn0000370	FBgn0000499	FBgn0003870	FBgn0025743	FBgn0039601
FBgn0003475	FBgn0086364	FBgn0015282	FBgn0028685	FBgn0032956	FBgn0259220
FBgn0039509	FBgn0032940	FBgn0010333	FBgn0014011	FBgn0025525	FBgn0038271
FBgn0000259	FBgn0000964	FBgn0031537	FBgn0026401	FBgn0000617	FBgn0053520
FBgn0036134	FBgn0035976	FBgn0085448	FBgn0004863	FBgn0001169	FBgn0020496
FBgn0002023	FBgn0011277	FBgn0028902	FBgn0008651	FBgn0004859	FBgn0033073
FBgn0013718	FBgn0014931	FBgn0001079	FBgn0004644	FBgn0004837	FBgn0004647
FBgn0003460	FBgn0000319	FBgn0039044	FBgn0035021	FBgn0001269	FBgn0259481
FBgn0031537	FBgn0015286	FBgn0002921	FBgn0053980	FBgn0003429	FBgn0004907
FBgn0024371	FBgn0038390	FBgn0026313	FBgn0028369	FBgn0024371	FBgn0036274
FBgn0003169	FBgn0011300	FBgn0000258	FBgn0025334	FBgn0010379	FBgn0025334
FBgn0000250	FBgn0024222	FBgn0004647	FBgn0034476	FBgn0001085	FBgn0000499
FBgn0011817	FBgn0085432	FBgn0002733	FBgn0004170	FBgn0004106	FBgn0011766
FBgn0024330	FBgn0038578	FBgn0004652	FBgn0011260	FBgn0000283	FBgn0026170
FBgn0024371	FBgn0028577	FBgn0025806	FBgn0038576	FBgn0041582	FBgn0260632
FBgn0010333	FBgn0030018	FBgn0003256	FBgn0016034	FBgn0011290	FBgn0000588
FBgn0260632	FBgn0260632	FBgn0028734	FBgn0002023	FBgn0003124	FBgn0010355
FBgn0004859	FBgn0086655	FBgn0003124	FBgn0000439	FBgn0028734	FBgn0039016
FBgn0025637	FBgn0035357	FBgn0013765	FBgn0035518	FBgn0010379	FBgn0008646
FBgn0010280	FBgn0010355	FBgn0001319	FBgn0053208	FBgn0003460	FBgn0000259
FBgn0003044	FBgn0003044	FBgn0014396	FBgn0086758	FBgn0011763	FBgn0011766
FBgn0025806	FBgn0021873	FBgn0003870	FBgn0011725	FBgn0003002	FBgn0050420
FBgn0031850	FBgn0053980	FBgn0000330	FBgn0025334	FBgn0037555	FBgn0039044
FBgn0066101	FBgn0011277	FBgn0032956	FBgn0000546	FBgn0000721	FBgn0086384
FBgn0037093	FBgn0000242	FBgn0004859	FBgn0003145	FBgn0001319	FBgn0014931
FBgn0024491	FBgn0024491	FBgn0000659	FBgn0000259	FBgn0038063	FBgn0000472
FBgn0026411	FBgn0024728	FBgn0027052	FBgn0036558	FBgn0085369	FBgn0011640
FBgn0000352	FBgn0086758	FBgn0052475	FBgn0031850	FBgn0015624	FBgn0003479
FBgn0003256	FBgn0028386	FBgn0029711	FBgn0020386	FBgn0000463	FBgn0003870
FBgn0000611	FBgn0003944	FBgn0015778	FBgn0003410	FBgn0019650	FBgn0023215
FBgn0004859	FBgn0025681	FBgn0013997	FBgn0243505	FBgn0015589	FBgn0000117
FBgn0003205	FBgn0003145	FBgn0003479	FBgn0023091	FBgn0025637	FBgn0025637
FBgn0086384	FBgn0003270	FBgn0000206	FBgn0003366	FBgn0023388	FBgn0010342
FBgn0024371	FBgn0042630	FBgn0038747	FBgn0000524	FBgn0013997	FBgn0067864
FBgn0002609	FBgn0002733	FBgn0086384	FBgn0086384	FBgn0032956	FBgn0035357
FBgn0051999	FBgn0053980	FBgn0003129	FBgn0004050	FBgn0034534	FBgn0000338
FBgn0002609	FBgn0002735	FBgn0031850	FBgn0001942	FBgn0000352	FBgn0000411
FBgn0002609	FBgn0002734	FBgn0005355	FBgn0004859	FBgn0010323	FBgn0001139
FBgn0034926	FBgn0024250	FBgn0024291	FBgn0000259	FBgn0000463	FBgn0000606
FBgn0039907	FBgn0085432	FBgn0013759	FBgn0024909	FBgn0026175	FBgn0015509
FBgn0024732	FBgn0001090	FBgn0086384	FBgn0011277	FBgn0013765	FBgn0039923
FBgn0003317	FBgn0020493	FBgn0034904	FBgn0015904	FBgn0034904	FBgn0000546
FBgn0030242	FBgn0031878	FBgn0000117	FBgn0038578	FBgn0000413	FBgn0004170
FBgn0002633	FBgn0002781	FBgn0259176	FBgn0013765	FBgn0011648	FBgn0003557
FBgn0010333	FBgn0039016	FBgn0014396	FBgn0039938	FBgn0023423	FBgn0015509
FBgn0002914	FBgn0024371	FBgn0025637	FBgn0000250	FBgn0011225	FBgn0020503

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in *D. melanogaster*-continued

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0002914	FBgn0038390	FBgn0027788	FBgn0000338	FBgn0011661	FBgn0011259
FBgn0031537	FBgn0001235	FBgn0010380	FBgn0011300	FBgn0040078	FBgn0087008
FBgn0000625	FBgn0003464	FBgn0001323	FBgn0024250	FBgn0003892	FBgn0259750
FBgn0000810	FBgn0001077	FBgn0031537	FBgn0000658	FBgn0041171	FBgn0003943
FBgn0053531	FBgn0003942	FBgn0013263	FBgn0013263	FBgn0029105	FBgn0011817
FBgn0003479	FBgn0011747	FBgn0000577	FBgn0011277	FBgn0003410	FBgn0260635
FBgn0000591	FBgn0001139	FBgn0035638	FBgn0032105	FBgn0086384	FBgn0067864
FBgn0002914	FBgn0011763	FBgn0010323	FBgn0003464	FBgn0002023	FBgn0003896
FBgn0002413	FBgn0023423	FBgn0003870	FBgn0013725	FBgn0027052	FBgn0000352
FBgn0031871	FBgn0250789	FBgn0004896	FBgn0036274	FBgn0015624	FBgn0025334
FBgn0011715	FBgn0032872	FBgn0003892	FBgn0022720	FBgn0003892	FBgn0003410
FBgn0037751	FBgn0019650	FBgn0017581	FBgn0025334	FBgn0003460	FBgn0037377
FBgn0020503	FBgn0028550	FBgn0001319	FBgn0010355	FBgn0039044	FBgn0053208
FBgn0000499	FBgn0003944	FBgn0003720	FBgn0004863	FBgn0002921	FBgn0024250
FBgn0003090	FBgn0003090	FBgn0001202	FBgn0024728	FBgn0013725	FBgn0030151
FBgn0000588	FBgn0020887	FBgn0029711	FBgn0026262	FBgn0003870	FBgn0016917
FBgn0010109	FBgn0027788	FBgn0003870	FBgn0008649	FBgn0000117	FBgn0003391
FBgn0011661	FBgn0001624	FBgn0019809	FBgn0004598	FBgn0004859	FBgn0005511
FBgn0001150	FBgn0020496	FBgn0028577	FBgn0259794	FBgn0004106	FBgn0011737
FBgn0034821	FBgn0011640	FBgn0000163	FBgn0022131	FBgn0022238	FBgn0026262
FBgn0041171	FBgn0001219	FBgn0001139	FBgn0010575	FBgn0003892	FBgn0020309
FBgn0039170	FBgn0026192	FBgn0010333	FBgn0026318	FBgn0034904	FBgn0259217
FBgn0010280	FBgn0037555	FBgn0022238	FBgn0003870	FBgn0000166	FBgn0024491
FBgn0046874	FBgn0023531	FBgn0039044	FBgn0003479	FBgn0030318	FBgn0003607
FBgn0051999	FBgn0020306	FBgn0031537	FBgn0004167	FBgn0027788	FBgn0015907
FBgn0260632	FBgn0053980	FBgn0031450	FBgn0000658	FBgn0004647	FBgn0003870
FBgn0023509	FBgn0024371	FBgn0011715	FBgn0003464	FBgn0085448	FBgn0000529
FBgn0003892	FBgn0052486	FBgn0002609	FBgn0002631	FBgn0002633	FBgn0011277
FBgn0086364	FBgn0037094	FBgn0001990	FBgn0001990	FBgn0000117	FBgn0015624
FBgn0035993	FBgn0005630	FBgn0051999	FBgn0001233	FBgn0019650	FBgn0016917
FBgn0000499	FBgn0013591	FBgn0002633	FBgn0000964	FBgn0011276	FBgn0024234
FBgn0000588	FBgn0003044	FBgn0000233	FBgn0011836	FBgn0086358	FBgn0000157
FBgn0086384	FBgn0003345	FBgn0038063	FBgn0023215	FBgn0002973	FBgn0022131
FBgn0003031	FBgn0020496	FBgn0030318	FBgn0025741	FBgn0000588	FBgn0000629
FBgn0000108	FBgn0026313	FBgn0003415	FBgn0015618	FBgn0004647	FBgn0015778
FBgn0003410	FBgn0003870	FBgn0004595	FBgn0010300	FBgn0031850	FBgn0019650
FBgn0036671	FBgn0002774	FBgn0000117	FBgn0003944	FBgn0025806	FBgn0004102
FBgn0008651	FBgn0040080	FBgn0001168	FBgn0020496	FBgn0030941	FBgn0033483
FBgn0031450	FBgn0000319	FBgn0010379	FBgn0000578	FBgn0000499	FBgn0003090
FBgn0010379	FBgn0003479	FBgn0025806	FBgn0026611	FBgn0003334	FBgn0004861
FBgn0086384	FBgn0087002	FBgn0259220	FBgn0259220	FBgn0000529	FBgn0004863
FBgn0041582	FBgn0001235	FBgn0013765	FBgn0002873	FBgn0003944	FBgn0017453
FBgn0010315	FBgn0000578	FBgn0031850	FBgn0004595	FBgn0041582	FBgn0041582
FBgn0039946	FBgn0026262	FBgn0024291	FBgn0002921	FBgn0000625	FBgn0035849
FBgn0086384	FBgn0038418	FBgn0023522	FBgn0003380	FBgn0039907	FBgn0043900
FBgn0003460	FBgn0039038	FBgn0002413	FBgn0003068	FBgn0003964	FBgn0023518
FBgn0015624	FBgn0042630	FBgn0000439	FBgn0000611	FBgn0010379	FBgn0019650
FBgn0259220	FBgn0025334	FBgn0066101	FBgn0003941	FBgn0025638	FBgn0032956
FBgn0000253	FBgn0036697	FBgn0015282	FBgn0036224	FBgn0003371	FBgn0000117
FBgn0027356	FBgn0259174	FBgn0000413	FBgn0002733	FBgn0000022	FBgn0002735
FBgn0011648	FBgn0004893	FBgn0001978	FBgn0001105	FBgn0003430	FBgn0011640
FBgn0001078	FBgn0004907	FBgn0000413	FBgn0002735	FBgn0259794	FBgn0053169
FBgn0003410	FBgn0052392	FBgn0040080	FBgn0015240	FBgn0004638	FBgn0016794
FBgn0011715	FBgn0011747	FBgn0026411	FBgn0037672	FBgn0011586	FBgn0041171

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in *D. melanogaster*-continued

Interactor A	**Interactor B**	**Interactor A**	**Interactor B**	**Interactor A**	**Interactor B**
FBgn0003326	FBgn0004647	FBgn0260632	FBgn0000250	FBgn0001978	FBgn0019650
FBgn0010379	FBgn0016081	FBgn0000459	FBgn0020496	FBgn0001150	FBgn0005630
FBgn0003124	FBgn0003270	FBgn0001222	FBgn0038578	FBgn0027788	FBgn0004598
FBgn0024330	FBgn0017578	FBgn0038576	FBgn0024194	FBgn0000042	FBgn0087008
FBgn0004638	FBgn0036274	FBgn0035956	FBgn0004863	FBgn0004647	FBgn0023215
FBgn0000097	FBgn0023214	FBgn0026562	FBgn0053980	FBgn0000022	FBgn0002733
FBgn0005355	FBgn0032475	FBgn0001319	FBgn0039283	FBgn0030318	FBgn0011640
FBgn0020496	FBgn0001320	FBgn0031878	FBgn0000611	FBgn0025680	FBgn0004102
FBgn0000163	FBgn0026192	FBgn0003892	FBgn0011606	FBgn0034904	FBgn0000578
FBgn0086384	FBgn0000250	FBgn0008646	FBgn0000490	FBgn0003460	FBgn0259750
FBgn0001079	FBgn0005355	FBgn0039044	FBgn0039923	FBgn0022382	FBgn0011291
FBgn0004861	FBgn0013263	FBgn0000182	FBgn0001120	FBgn0011763	FBgn0015799
FBgn0001323	FBgn0053980	FBgn0001139	FBgn0085432	FBgn0025458	FBgn0001994
FBgn0020496	FBgn0001325	FBgn0011763	FBgn0024371	FBgn0001168	FBgn0010109
FBgn0022131	FBgn0024250	FBgn0002733	FBgn0015550	FBgn0004510	FBgn0013725
FBgn0010315	FBgn0000166	FBgn0010379	FBgn0000546	FBgn0004858	FBgn0000258
FBgn0031850	FBgn0015589	FBgn0027052	FBgn0000250	FBgn0031450	FBgn0011202
FBgn0003986	FBgn0000182	FBgn0001319	FBgn0003870	FBgn0001133	FBgn0033081
FBgn0025637	FBgn0023423	FBgn0011771	FBgn0001990	FBgn0003479	FBgn0053208
FBgn0015799	FBgn0023509	FBgn0000212	FBgn0003013	FBgn0038747	FBgn0039066
FBgn0015790	FBgn0013725	FBgn0000392	FBgn0026577	FBgn0000117	FBgn0015609
FBgn0011661	FBgn0010110	FBgn0025638	FBgn0024250	FBgn0000591	FBgn0000591
FBgn0010315	FBgn0000546	FBgn0019809	FBgn0011260	FBgn0013765	FBgn0000524
FBgn0000114	FBgn0004882	FBgn0002631	FBgn0015550	FBgn0036671	FBgn0013765
FBgn0000229	FBgn0011737	FBgn0038852	FBgn0015904	FBgn0000283	FBgn0003567
FBgn0003892	FBgn0250786	FBgn0034904	FBgn0011586	FBgn0011763	FBgn0038390
FBgn0028577	FBgn0000319	FBgn0003002	FBgn0259794	FBgn0003600	FBgn0003607
FBgn0014396	FBgn0010355	FBgn0035638	FBgn0038439	FBgn0003870	FBgn0023444
FBgn0031850	FBgn0000504	FBgn0086358	FBgn0026323	FBgn0026598	FBgn0000117
FBgn0005355	FBgn0003862	FBgn0086358	FBgn0000114	FBgn0027788	FBgn0000524
FBgn0032956	FBgn0023091	FBgn0001079	FBgn0010825	FBgn0014931	FBgn0014931
FBgn0013765	FBgn0259794	FBgn0000629	FBgn0020887	FBgn0259220	FBgn0003479
FBgn0024321	FBgn0020496	FBgn0066101	FBgn0259481	FBgn0000629	FBgn0003044
FBgn0002631	FBgn0002733	FBgn0004859	FBgn0000179	FBgn0010341	FBgn0025743
FBgn0000414	FBgn0003366	FBgn0002609	FBgn0001139	FBgn0000352	FBgn0015396
FBgn0002631	FBgn0002734	FBgn0000964	FBgn0034802	FBgn0000212	FBgn0004050
FBgn0005630	FBgn0026262	FBgn0051999	FBgn0000504	FBgn0026318	FBgn0011277
FBgn0002631	FBgn0002735	FBgn0024732	FBgn0028408	FBgn0013984	FBgn0013984
FBgn0000611	FBgn0001235	FBgn0010333	FBgn0020621	FBgn0014396	FBgn0000179
FBgn0000229	FBgn0086358	FBgn0041582	FBgn0013725	FBgn0027788	FBgn0052392
FBgn0010380	FBgn0016797	FBgn0013725	FBgn0004907	FBgn0000382	FBgn0016794
FBgn0025458	FBgn0005630	FBgn0011715	FBgn0087008	FBgn0011715	FBgn0000547
FBgn0028407	FBgn0036254	FBgn0085448	FBgn0015903	FBgn0000137	FBgn0002609
FBgn0010379	FBgn0038197	FBgn0024330	FBgn0022740	FBgn0002941	FBgn0259794
FBgn0015805	FBgn0020887	FBgn0011661	FBgn0026056	FBgn0025637	FBgn0041171
FBgn0032202	FBgn0039209	FBgn0010315	FBgn0023091	FBgn0026562	FBgn0086680
FBgn0001170	FBgn0037094	FBgn0038852	FBgn0004863	FBgn0004859	FBgn0000242
FBgn0000529	FBgn0002940	FBgn0019686	FBgn0259220	FBgn0015624	FBgn0000157
FBgn0003124	FBgn0028789	FBgn0035993	FBgn0029905	FBgn0001150	FBgn0032202
FBgn0001170	FBgn0001139	FBgn0086364	FBgn0035849	FBgn0259794	FBgn0013725
FBgn0023215	FBgn0017578	FBgn0000472	FBgn0041171	FBgn0013725	FBgn0013725
FBgn0001139	FBgn0020496	FBgn0003044	FBgn0015805	FBgn0003002	FBgn0025334
FBgn0003013	FBgn0040078	FBgn0260632	FBgn0003942	FBgn0066101	FBgn0015778
FBgn0033998	FBgn0004863	FBgn0003479	FBgn0026262	FBgn0024510	FBgn0243505

Table C.1. Protein-protein interactions in Wnt/β-catenin signaling network in *D. melanogaster*-continued

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0001319	FBgn0024510	FBgn0010441	FBgn0260632	FBgn0002733	FBgn0010433
FBgn0086384	FBgn0053519	FBgn0013750	FBgn0026056	FBgn0004896	FBgn0038271
FBgn0000212	FBgn0011715	FBgn0019947	FBgn0000117	FBgn0025458	FBgn0086384
FBgn0000964	FBgn0000964	FBgn0002973	FBgn0026192	FBgn0042630	FBgn0031850
FBgn0000061	FBgn0003944	FBgn0000546	FBgn0023518	FBgn0004837	FBgn0010110
FBgn0004859	FBgn0004167	FBgn0000166	FBgn0003870	FBgn0031450	FBgn0027356
FBgn0000578	FBgn0004638	FBgn0025806	FBgn0015609	FBgn0000463	FBgn0000283
FBgn0020386	FBgn0086910	FBgn0001078	FBgn0001077	FBgn0004647	FBgn0086758
FBgn0029905	FBgn0000042	FBgn0002734	FBgn0020496	FBgn0028902	FBgn0022740
FBgn0031537	FBgn0004907	FBgn0011715	FBgn0040078	FBgn0013725	FBgn0023444
FBgn0004859	FBgn0015624	FBgn0003862	FBgn0003862	FBgn0001319	FBgn0003270
FBgn0003013	FBgn0087008	FBgn0003716	FBgn0020493	FBgn0000499	FBgn0003567
FBgn0086384	FBgn0002921	FBgn0010333	FBgn0000319	FBgn0010194	FBgn0015380
FBgn0086384	FBgn0026262	FBgn0000463	FBgn0086442	FBgn0004915	FBgn0022740
FBgn0019650	FBgn0250788	FBgn0000617	FBgn0037555	FBgn0024222	FBgn0024222
FBgn0086358	FBgn0025334	FBgn0260632	FBgn0038659	FBgn0011766	FBgn0015799
FBgn0000629	FBgn0024491	FBgn0000163	FBgn0026319	FBgn0000163	FBgn0002973
FBgn0000588	FBgn0000588	FBgn0015286	FBgn0026056	FBgn0025632	FBgn0000042
FBgn0015286	FBgn0005558	FBgn0015778	FBgn0014931	FBgn0000114	FBgn0015903
FBgn0001139	FBgn0026192	FBgn0041171	FBgn0052133	FBgn0041171	FBgn0000490
FBgn0001981	FBgn0013765	FBgn0024371	FBgn0000611	FBgn0028685	FBgn0028687
FBgn0003944	FBgn0015903	FBgn0003479	FBgn0035357	FBgn0243505	FBgn0259685
FBgn0000591	FBgn0002631	FBgn0000259	FBgn0000258	FBgn0260632	FBgn0001990
FBgn0001170	FBgn0046874	FBgn0030695	FBgn0030695	FBgn0028407	FBgn0002932
FBgn0029905	FBgn0016917	FBgn0001078	FBgn0000411	FBgn0024222	FBgn0041205
FBgn0000591	FBgn0002633	FBgn0020369	FBgn0015282	FBgn0028685	FBgn0028685
FBgn0003479	FBgn0003612	FBgn0003068	FBgn0014396	FBgn0019650	FBgn0002968
FBgn0004859	FBgn0003415	FBgn0004859	FBgn0004859	FBgn0003479	FBgn0039923
FBgn0000611	FBgn0003339	FBgn0023531	FBgn0004624	FBgn0011715	FBgn0000524
FBgn0053520	FBgn0000346	FBgn0004859	FBgn0004858	FBgn0013725	FBgn0003410
FBgn0000547	FBgn0002968	FBgn0003118	FBgn0003256	FBgn0004647	FBgn0031450
FBgn0025637	FBgn0021875	FBgn0036497	FBgn0027052	FBgn0000352	FBgn0004859
FBgn0000463	FBgn0004647	FBgn0086384	FBgn0259234	FBgn0041582	FBgn0024250
FBgn0039044	FBgn0033636	FBgn0000413	FBgn0000575	FBgn0003475	FBgn0003317
FBgn0000392	FBgn0001219	FBgn0026080	FBgn0004863	FBgn0002609	FBgn0004170
FBgn0003941	FBgn0003942	FBgn0000560	FBgn0002631	FBgn0000499	FBgn0002945
FBgn0023091	FBgn0052486	FBgn0001133	FBgn0035769	FBgn0066101	FBgn0000472
FBgn0052486	FBgn0005694	FBgn0003124	FBgn0036799	FBgn0000210	FBgn0046874
FBgn0025637	FBgn0259220	FBgn0004837	FBgn0037475	FBgn0004859	FBgn0005771
FBgn0022238	FBgn0013263	FBgn0061173	FBgn0002940	FBgn0026404	FBgn0260635
FBgn0026313	FBgn0040466	FBgn0086384	FBgn0003145	FBgn0000283	FBgn0010342
FBgn0001978	FBgn0033029	FBgn0000617	FBgn0010417	FBgn0025637	FBgn0038206
FBgn0031985	FBgn0004907	FBgn0010287	FBgn0024371	FBgn0003892	FBgn0026313
FBgn0000463	FBgn0003520	FBgn0000392	FBgn0015778	FBgn0004009	FBgn0000119
FBgn0031450	FBgn0030749	FBgn0026404	FBgn0003870	FBgn0028577	FBgn0000042
FBgn0026411	FBgn0000042	FBgn0004009	FBgn0016797	FBgn0000499	FBgn0052532
FBgn0000042	FBgn0011715	FBgn0259220	FBgn0019650	FBgn0000629	FBgn0015805
FBgn0086384	FBgn0003512	FBgn0026597	FBgn0015589	FBgn0003124	FBgn0042650
FBgn0004895	FBgn0004863	FBgn0002735	FBgn0002735		

Table C.2. Protein-protein interactions in Hedgehog signaling network in *D. melanogaster*

Interactor A	**Interactor B**	**Interactor A**	**Interactor B**	**Interactor A**	**Interactor B**
FBgn0003124	FBgn0000179	FBgn0025637	FBgn0259220	FBgn0004837	FBgn0037475
FBgn0001168	FBgn0003944	FBgn0022238	FBgn0013263	FBgn0061173	FBgn0002940
FBgn0028734	FBgn0003896	FBgn0031985	FBgn0004907	FBgn0086384	FBgn0003145
FBgn0015381	FBgn0027338	FBgn0000463	FBgn0003520	FBgn0000392	FBgn0015778
FBgn0015024	FBgn0003444	FBgn0004859	FBgn0053548	FBgn0026404	FBgn0003870
FBgn0000413	FBgn0002633	FBgn0026411	FBgn0000042	FBgn0259220	FBgn0019650
FBgn0000413	FBgn0002631	FBgn0086384	FBgn0003512	FBgn0002735	FBgn0002735
FBgn0020496	FBgn0023444	FBgn0004895	FBgn0004863	FBgn0002609	FBgn0002609
FBgn0024371	FBgn0000166	FBgn0000258	FBgn0260934	FBgn0004858	FBgn0038852
FBgn0086358	FBgn0038271	FBgn0000233	FBgn0010280	FBgn0004859	FBgn0001078
FBgn0004859	FBgn0038271	FBgn0004644	FBgn0040388	FBgn0011661	FBgn0011661
FBgn0000721	FBgn0005630	FBgn0003410	FBgn0013765	FBgn0004859	FBgn0027535
FBgn0025637	FBgn0000166	FBgn0028577	FBgn0038271	FBgn0004859	FBgn0013759
FBgn0001168	FBgn0001168	FBgn0019686	FBgn0023091	FBgn0001079	FBgn0019968
FBgn0000182	FBgn0004882	FBgn0000588	FBgn0015805	FBgn0003118	FBgn0023214
FBgn0027574	FBgn0020386	FBgn0001139	FBgn0002631	FBgn0032492	FBgn0036224
FBgn0001323	FBgn0001624	FBgn0001139	FBgn0002633	FBgn0001139	FBgn0001168
FBgn0001324	FBgn0015618	FBgn0003892	FBgn0042630	FBgn0023423	FBgn0026175
FBgn0011661	FBgn0034400	FBgn0039044	FBgn0023091	FBgn0001120	FBgn0000338
FBgn0013725	FBgn0001233	FBgn0004895	FBgn0004870	FBgn0014143	FBgn0039286
FBgn0000352	FBgn0003371	FBgn0011661	FBgn0013984	FBgn0000137	FBgn0000575
FBgn0004106	FBgn0010315	FBgn0008646	FBgn0011640	FBgn0004859	FBgn0039283
FBgn0039044	FBgn0000166	FBgn0003892	FBgn0003328	FBgn0015282	FBgn0000229
FBgn0019650	FBgn0001219	FBgn0002781	FBgn0013263	FBgn0000259	FBgn0011277
FBgn0011648	FBgn0011655	FBgn0025637	FBgn0033260	FBgn0000273	FBgn0003429
FBgn0020255	FBgn0041582	FBgn0003371	FBgn0015589	FBgn0020369	FBgn0035849
FBgn0000229	FBgn0003464	FBgn0037555	FBgn0053520	FBgn0004859	FBgn0086902
FBgn0002973	FBgn0015567	FBgn0003892	FBgn0053208	FBgn0000251	FBgn0000258
FBgn0004870	FBgn0250785	FBgn0019650	FBgn0003345	FBgn0011300	FBgn0053967
FBgn0011771	FBgn0020510	FBgn0037555	FBgn0037981	FBgn0000413	FBgn0000591
FBgn0001319	FBgn0003345	FBgn0003943	FBgn0031450	FBgn0036697	FBgn0001320
FBgn0004647	FBgn0011591	FBgn0000629	FBgn0000629	FBgn0023388	FBgn0004598
FBgn0003687	FBgn0037555	FBgn0000504	FBgn0037811	FBgn0013765	FBgn0000273
FBgn0000042	FBgn0000212	FBgn0029878	FBgn0036274	FBgn0000251	FBgn0001308
FBgn0026411	FBgn0003464	FBgn0039044	FBgn0010602	FBgn0005630	FBgn0005630
FBgn0000166	FBgn0000439	FBgn0001079	FBgn0000028	FBgn0035993	FBgn0004606
FBgn0001981	FBgn0020496	FBgn0010379	FBgn0001148	FBgn0028642	FBgn0013718
FBgn0003870	FBgn0259794	FBgn0003479	FBgn0033636	FBgn0003068	FBgn0023423
FBgn0003254	FBgn0022238	FBgn0003944	FBgn0013591	FBgn0031450	FBgn0020496
FBgn0041582	FBgn0000611	FBgn0004859	FBgn0003425	FBgn0003892	FBgn0010602
FBgn0024184	FBgn0001139	FBgn0038747	FBgn0003464	FBgn0002121	FBgn0022131
FBgn0010379	FBgn0042630	FBgn0028577	FBgn0250848	FBgn0004859	FBgn0001235
FBgn0041171	FBgn0025741	FBgn0042630	FBgn0003942	FBgn0003124	FBgn0015550
FBgn0001170	FBgn0002940	FBgn0010315	FBgn0008646	FBgn0010602	FBgn0004050
FBgn0000166	FBgn0015602	FBgn0031450	FBgn0250788	FBgn0260632	FBgn0000504
FBgn0002609	FBgn0010433	FBgn0002734	FBgn0002734	FBgn0015331	FBgn0000338
FBgn0086384	FBgn0039283	FBgn0002734	FBgn0002735	FBgn0037466	FBgn0259794
FBgn0000499	FBgn0005558	FBgn0015624	FBgn0023091	FBgn0086364	FBgn0030343
FBgn0000229	FBgn0003475	FBgn0086384	FBgn0015371	FBgn0015024	FBgn0004859
FBgn0004896	FBgn0000524	FBgn0003002	FBgn0003464	FBgn0041171	FBgn0011260
FBgn0011661	FBgn0051619	FBgn0028642	FBgn0026597	FBgn0086384	FBgn0011661
FBgn0010235	FBgn0000497	FBgn0086358	FBgn0002985	FBgn0031450	FBgn0001235
FBgn0027788	FBgn0034160	FBgn0000042	FBgn0011771	FBgn0004896	FBgn0039066
FBgn0085448	FBgn0250848	FBgn0010109	FBgn0010109	FBgn0000463	FBgn0039283
FBgn0003720	FBgn0020496	FBgn0000166	FBgn0004893	FBgn0019650	FBgn0000448

Table C.2. Protein-protein interactions in Hedgehog signaling network in *D. melanogaster*-continued

Interactor A	**Interactor B**	**Interactor A**	**Interactor B**	**Interactor A**	**Interactor B**
FBgn0029711	FBgn0051619	FBgn0259220	FBgn0023091	FBgn0013765	FBgn0000250
FBgn0008651	FBgn0036274	FBgn0003124	FBgn0004394	FBgn0023215	FBgn0029114
FBgn0028577	FBgn0013725	FBgn0027609	FBgn0025637	FBgn0003448	FBgn0020496
FBgn0028734	FBgn0028734	FBgn0003129	FBgn0026170	FBgn0004859	FBgn0004607
FBgn0086897	FBgn0039038	FBgn0000212	FBgn0087008	FBgn0029711	FBgn0038341
FBgn0000166	FBgn0033073	FBgn0011648	FBgn0000166	FBgn0003600	FBgn0015805
FBgn0259220	FBgn0010602	FBgn0053967	FBgn0086358	FBgn0010235	FBgn0010235
FBgn0004647	FBgn0000179	FBgn0011661	FBgn0036254	FBgn0011648	FBgn0041582
FBgn0035938	FBgn0010602	FBgn0003892	FBgn0000546	FBgn0003892	FBgn0259217
FBgn0011276	FBgn0000413	FBgn0003892	FBgn0030600	FBgn0004647	FBgn0085445
FBgn0015024	FBgn0015589	FBgn0050011	FBgn0024491	FBgn0036497	FBgn0041582
FBgn0000560	FBgn0020496	FBgn0003429	FBgn0024728	FBgn0003448	FBgn0023444
FBgn0038852	FBgn0000182	FBgn0004859	FBgn0028789	FBgn0010235	FBgn0001308
FBgn0003410	FBgn0003410	FBgn0001085	FBgn0024836	FBgn0000258	FBgn0002633
FBgn0000499	FBgn0004647	FBgn0001168	FBgn0002609	FBgn0003892	FBgn0003896
FBgn0005558	FBgn0003607	FBgn0024432	FBgn0004598	FBgn0004510	FBgn0000472
FBgn0029905	FBgn0035993	FBgn0005771	FBgn0040918	FBgn0003892	FBgn0003892
FBgn0032651	FBgn0008635	FBgn0250843	FBgn0015282	FBgn0003334	FBgn0003334
FBgn0008651	FBgn0001139	FBgn0000022	FBgn0002609	FBgn0000382	FBgn0004907
FBgn0002121	FBgn0026192	FBgn0027356	FBgn0027356	FBgn0020496	FBgn0024250
FBgn0015014	FBgn0015542	FBgn0003460	FBgn0004863	FBgn0011737	FBgn0030695
FBgn0011648	FBgn0002973	FBgn0003256	FBgn0003256	FBgn0003944	FBgn0022720
FBgn0011661	FBgn0003942	FBgn0053520	FBgn0004863	FBgn0085410	FBgn0000042
FBgn0003430	FBgn0001139	FBgn0013263	FBgn0024491	FBgn0001120	FBgn0024250
FBgn0004666	FBgn0015014	FBgn0024371	FBgn0025334	FBgn0000137	FBgn0002633
FBgn0024371	FBgn0016081	FBgn0000577	FBgn0022720	FBgn0003430	FBgn0038271
FBgn0041582	FBgn0053980	FBgn0010235	FBgn0013718	FBgn0003345	FBgn0028999
FBgn0004914	FBgn0015542	FBgn0260632	FBgn0035989	FBgn0011648	FBgn0053936
FBgn0001319	FBgn0000606	FBgn0000166	FBgn0036274	FBgn0004859	FBgn0001320
FBgn0033015	FBgn0011277	FBgn0020381	FBgn0038928	FBgn0023531	FBgn0020510
FBgn0003479	FBgn0003479	FBgn0000964	FBgn0016797	FBgn0004510	FBgn0260934
FBgn0015371	FBgn0001233	FBgn0022131	FBgn0026192	FBgn0035993	FBgn0035993
FBgn0031450	FBgn0001324	FBgn0000352	FBgn0015024	FBgn0004644	FBgn0031872
FBgn0008651	FBgn0003464	FBgn0003892	FBgn0259174	FBgn0000617	FBgn0037981
FBgn0024371	FBgn0015904	FBgn0031985	FBgn0001308	FBgn0001319	FBgn0033636
FBgn0010323	FBgn0039936	FBgn0002735	FBgn0004170	FBgn0011661	FBgn0087008
FBgn0003124	FBgn0016977	FBgn0052486	FBgn0052486	FBgn0001139	FBgn0002735
FBgn0024371	FBgn0000546	FBgn0004859	FBgn0004387	FBgn0001139	FBgn0002734
FBgn0041582	FBgn0001990	FBgn0000575	FBgn0011277	FBgn0000964	FBgn0002985
FBgn0015624	FBgn0008646	FBgn0005630	FBgn0015903	FBgn0001139	FBgn0002733
FBgn0003511	FBgn0250785	FBgn0000117	FBgn0039907	FBgn0086384	FBgn0010452
FBgn0003892	FBgn0011300	FBgn0028642	FBgn0002521	FBgn0019650	FBgn0003651
FBgn0004647	FBgn0036558	FBgn0013765	FBgn0022720	FBgn0020496	FBgn0039283
FBgn0011661	FBgn0004606	FBgn0003900	FBgn0260632	FBgn0001202	FBgn0011277
FBgn0000259	FBgn0000524	FBgn0031450	FBgn0024191	FBgn0000413	FBgn0000413
FBgn0015778	FBgn0259794	FBgn0001079	FBgn0010110	FBgn0000629	FBgn0001219
FBgn0050011	FBgn0050011	FBgn0041582	FBgn0000504	FBgn0035938	FBgn0003479
FBgn0003425	FBgn0005631	FBgn0015903	FBgn0015903	FBgn0003687	FBgn0053520
FBgn0004859	FBgn0002413	FBgn0002781	FBgn0026170	FBgn0022238	FBgn0011236
FBgn0001079	FBgn0000352	FBgn0019686	FBgn0010602	FBgn0000028	FBgn0086680
FBgn0028734	FBgn0000250	FBgn0002023	FBgn0024321	FBgn0019650	FBgn0000490
FBgn0002723	FBgn0001308	FBgn0026411	FBgn0000259	FBgn0002631	FBgn0002631
FBgn0003460	FBgn0001139	FBgn0002633	FBgn0010433	FBgn0002631	FBgn0002633
FBgn0086384	FBgn0023215	FBgn0003870	FBgn0010602	FBgn0000212	FBgn0001219

Table C.2. Protein-protein interactions in Hedgehog signaling network in *D. melanogaster*-continued

Interactor A	Interactor B	Interactor A	Interactor B	Interactor A	Interactor B
FBgn0040388	FBgn0031872	FBgn0000575	FBgn0004170	FBgn0003892	FBgn0004915
FBgn0003892	FBgn0016797	FBgn0000352	FBgn0003444	FBgn0038747	FBgn0002985
FBgn0000499	FBgn0053208	FBgn0025637	FBgn0015600	FBgn0001323	FBgn0020496
FBgn0016977	FBgn0037093	FBgn0259794	FBgn0039936	FBgn0020381	FBgn0086902
FBgn0003371	FBgn0004859	FBgn0011648	FBgn0004053	FBgn0019650	FBgn0036349
FBgn0086358	FBgn0004595	FBgn0003892	FBgn0003502	FBgn0086384	FBgn0003870
FBgn0085369	FBgn0001990	FBgn0001319	FBgn0003977	FBgn0001120	FBgn0001085
FBgn0003129	FBgn0011577	FBgn0003124	FBgn0002922	FBgn0002733	FBgn0002733
FBgn0002633	FBgn0004170	FBgn0015509	FBgn0025637	FBgn0002733	FBgn0002734
FBgn0001324	FBgn0003415	FBgn0015509	FBgn0025638	FBgn0002733	FBgn0002735
FBgn0001078	FBgn0028386	FBgn0035938	FBgn0025334	FBgn0010323	FBgn0086711
FBgn0030899	FBgn0001139	FBgn0019809	FBgn0052280	FBgn0000137	FBgn0002733
FBgn0027052	FBgn0001219	FBgn0000588	FBgn0024491	FBgn0000137	FBgn0002735
FBgn0001291	FBgn0028550	FBgn0000964	FBgn0003464	FBgn0005771	FBgn0005771
FBgn0004907	FBgn0259794	FBgn0039044	FBgn0035849	FBgn0001981	FBgn0000524
FBgn0015602	FBgn0015602	FBgn0259220	FBgn0004878	FBgn0260632	FBgn0020496
FBgn0010602	FBgn0040466	FBgn0000114	FBgn0000392	FBgn0003892	FBgn0003479
FBgn0028734	FBgn0036274	FBgn0003464	FBgn0024250	FBgn0028642	FBgn0259794
FBgn0003749	FBgn0015014	FBgn0004859	FBgn0000114	FBgn0000258	FBgn0002631
FBgn0086384	FBgn0002780	FBgn0037981	FBgn0053520	FBgn0031878	FBgn0000140
FBgn0040466	FBgn0260632	FBgn0003124	FBgn0039601	FBgn0001319	FBgn0042650
FBgn0010379	FBgn0259217	FBgn0025458	FBgn0029708	FBgn0086384	FBgn0003448
FBgn0000338	FBgn0034534	FBgn0028734	FBgn0027052	FBgn0011674	FBgn0026319
FBgn0004510	FBgn0052343	FBgn0004859	FBgn0002922	FBgn0000251	FBgn0005771
FBgn0041582	FBgn0000042	FBgn0010109	FBgn0001139	FBgn0000591	FBgn0002735
FBgn0020369	FBgn0036224	FBgn0004896	FBgn0021760	FBgn0000591	FBgn0002734
FBgn0086384	FBgn0010355	FBgn0003002	FBgn0044323	FBgn0000591	FBgn0002733
FBgn0003892	FBgn0002924	FBgn0000414	FBgn0004638	FBgn0000258	FBgn0000591
FBgn0011661	FBgn0039209	FBgn0001319	FBgn0003053	FBgn0010323	FBgn0000529
FBgn0013718	FBgn0003464	FBgn0028577	FBgn0003942	FBgn0003892	FBgn0003448
FBgn0001269	FBgn0001139	FBgn0000250	FBgn0000250	FBgn0026611	FBgn0039016
FBgn0003944	FBgn0005771	FBgn0023423	FBgn0004859	FBgn0003892	FBgn0003444
FBgn0002633	FBgn0002734	FBgn0000022	FBgn0002633	FBgn0001981	FBgn0010391
FBgn0002633	FBgn0002733	FBgn0003986	FBgn0024245	FBgn0001291	FBgn0003124
FBgn0039946	FBgn0011260	FBgn0027548	FBgn0000611	FBgn0000964	FBgn0002932
FBgn0002633	FBgn0002735	FBgn0000382	FBgn0003366	FBgn0023215	FBgn0021760
FBgn0086384	FBgn0010349	FBgn0259794	FBgn0000289	FBgn0001139	FBgn0003300
FBgn0027788	FBgn0004861	FBgn0002932	FBgn0004197	FBgn0017578	FBgn0000472
FBgn0005355	FBgn0039936	FBgn0020369	FBgn0013765	FBgn0010280	FBgn0013263
FBgn0019650	FBgn0004364	FBgn0028685	FBgn0036224	FBgn0003977	FBgn0000182
FBgn0011648	FBgn0039286	FBgn0259794	FBgn0027066	FBgn0003371	FBgn0025680
FBgn0000529	FBgn0020224	FBgn0001079	FBgn0004859	FBgn0035954	FBgn0002023
FBgn0003460	FBgn0046874	FBgn0002940	FBgn0003861	FBgn0026170	FBgn0260632
FBgn0085369	FBgn0086384	FBgn0025638	FBgn0033260	FBgn0020369	FBgn0028685
FBgn0013765	FBgn0002914	FBgn0003892	FBgn0011661	FBgn0000577	FBgn0003464
FBgn0260632	FBgn0004638	FBgn0035424	FBgn0010300	FBgn0001291	FBgn0001297
FBgn0004859	FBgn0030018	FBgn0004859	FBgn0027343	FBgn0020369	FBgn0028687
FBgn0031851	FBgn0001990	FBgn0003410	FBgn0001308	FBgn0031450	FBgn0000250
FBgn0036134	FBgn0259794	FBgn0024371	FBgn0259217	FBgn0001079	FBgn0003444
FBgn0038747	FBgn0032202	FBgn0086384	FBgn0015509	FBgn0001291	FBgn0001291
FBgn0003410	FBgn0023444	FBgn0004907	FBgn0003464	FBgn0025637	FBgn0002791
FBgn0086358	FBgn0259794	FBgn0086384	FBgn0053967	FBgn0032956	FBgn0259220
FBgn0004512	FBgn0014931	FBgn0086384	FBgn0032467	FBgn0005355	FBgn0001079
FBgn0024371	FBgn0004863	FBgn0005771	FBgn0000042	FBgn0025525	FBgn0038271

Table C.2. Protein-protein interactions in Hedgehog signaling network in *D. melanogaster*-continued

Interactor A	**Interactor B**	**Interactor A**	**Interactor B**	**Interactor A**	**Interactor B**
FBgn0020369	FBgn0002985	FBgn0037937	FBgn0000413	FBgn0000617	FBgn0053520
FBgn0001219	FBgn0003944	FBgn0000259	FBgn0008649	FBgn0004859	FBgn0033073
FBgn0004858	FBgn0003002	FBgn0015282	FBgn0028687	FBgn0004837	FBgn0004647
FBgn0000413	FBgn0010109	FBgn0035849	FBgn0015542	FBgn0003429	FBgn0004907
FBgn0005631	FBgn0005631	FBgn0000499	FBgn0003870	FBgn0001269	FBgn0259481
FBgn0000524	FBgn0004647	FBgn0015282	FBgn0028685	FBgn0024371	FBgn0036274
FBgn0000591	FBgn0001168	FBgn0085448	FBgn0004863	FBgn0010379	FBgn0025334
FBgn0024846	FBgn0003511	FBgn0010602	FBgn0260632	FBgn0004106	FBgn0011766
FBgn0000504	FBgn0046874	FBgn0001079	FBgn0004644	FBgn0041582	FBgn0260632
FBgn0000463	FBgn0010355	FBgn0039044	FBgn0035021	FBgn0003124	FBgn0010355
FBgn0000560	FBgn0002733	FBgn0000258	FBgn0025334	FBgn0028734	FBgn0039016
FBgn0032651	FBgn0024432	FBgn0004647	FBgn0034476	FBgn0010379	FBgn0008646
FBgn0013718	FBgn0000370	FBgn0002733	FBgn0004170	FBgn0003460	FBgn0000259
FBgn0003475	FBgn0086364	FBgn0011661	FBgn0003023	FBgn0011763	FBgn0011766
FBgn0000259	FBgn0000964	FBgn0019650	FBgn0027338	FBgn0037555	FBgn0039044
FBgn0013718	FBgn0014931	FBgn0028734	FBgn0002023	FBgn0000721	FBgn0086384
FBgn0002023	FBgn0011277	FBgn0003124	FBgn0000439	FBgn0004959	FBgn0034802
FBgn0003169	FBgn0011300	FBgn0013765	FBgn0035518	FBgn0001319	FBgn0014931
FBgn0000250	FBgn0024222	FBgn0001319	FBgn0053208	FBgn0000338	FBgn0027338
FBgn0024371	FBgn0028577	FBgn0003870	FBgn0011725	FBgn0038063	FBgn0000472
FBgn0260632	FBgn0260632	FBgn0032956	FBgn0000546	FBgn0085369	FBgn0011640
FBgn0004859	FBgn0086655	FBgn0032956	FBgn0010602	FBgn0015624	FBgn0003479
FBgn0010280	FBgn0010355	FBgn0004859	FBgn0003145	FBgn0000463	FBgn0003870
FBgn0034728	FBgn0001308	FBgn0000659	FBgn0000259	FBgn0019650	FBgn0023215
FBgn0037093	FBgn0000242	FBgn0027052	FBgn0036558	FBgn0029878	FBgn0013718
FBgn0024491	FBgn0024491	FBgn0000273	FBgn0003444	FBgn0025637	FBgn0025637
FBgn0026411	FBgn0024728	FBgn0029711	FBgn0020386	FBgn0001077	FBgn0001078
FBgn0003256	FBgn0028386	FBgn0015778	FBgn0003410	FBgn0000352	FBgn0000411
FBgn0000611	FBgn0003944	FBgn0003479	FBgn0023091	FBgn0010323	FBgn0001139
FBgn0004859	FBgn0025681	FBgn0004859	FBgn0027338	FBgn0000463	FBgn0000606
FBgn0024191	FBgn0003464	FBgn0000206	FBgn0003366	FBgn0013765	FBgn0039923
FBgn0024371	FBgn0042630	FBgn0038747	FBgn0000524	FBgn0034904	FBgn0000546
FBgn0086384	FBgn0003270	FBgn0086384	FBgn0086384	FBgn0000250	FBgn0010602
FBgn0002609	FBgn0002733	FBgn0003129	FBgn0004050	FBgn0000413	FBgn0004170
FBgn0002609	FBgn0002735	FBgn0024291	FBgn0000259	FBgn0023423	FBgn0015509
FBgn0002609	FBgn0002734	FBgn0013759	FBgn0024909	FBgn0013725	FBgn0003870
FBgn0034926	FBgn0024250	FBgn0024191	FBgn0039767	FBgn0003380	FBgn0001624
FBgn0002633	FBgn0002781	FBgn0086384	FBgn0011277	FBgn0011661	FBgn0011259
FBgn0002914	FBgn0024371	FBgn0034904	FBgn0015904	FBgn0029905	FBgn0250848
FBgn0024191	FBgn0022720	FBgn0003545	FBgn0011277	FBgn0003892	FBgn0259750
FBgn0053531	FBgn0003942	FBgn0259176	FBgn0013765	FBgn0041171	FBgn0003943
FBgn0003479	FBgn0011747	FBgn0014396	FBgn0039938	FBgn0086384	FBgn0019968
FBgn0000591	FBgn0001139	FBgn0027788	FBgn0000338	FBgn0027052	FBgn0000352
FBgn0002914	FBgn0011763	FBgn0025637	FBgn0000250	FBgn0002023	FBgn0003896
FBgn0002413	FBgn0023423	FBgn0001323	FBgn0024250	FBgn0015624	FBgn0025334
FBgn0037751	FBgn0019650	FBgn0013263	FBgn0013263	FBgn0004644	FBgn0003892
FBgn0000499	FBgn0003944	FBgn0000577	FBgn0011277	FBgn0003892	FBgn0003410
FBgn0003090	FBgn0003090	FBgn0010323	FBgn0003464	FBgn0003460	FBgn0037377
FBgn0000588	FBgn0020887	FBgn0004896	FBgn0036274	FBgn0039044	FBgn0053208
FBgn0010109	FBgn0027788	FBgn0003892	FBgn0022720	FBgn0003870	FBgn0016917
FBgn0011661	FBgn0001624	FBgn0017581	FBgn0025334	FBgn0000117	FBgn0003391
FBgn0001150	FBgn0020496	FBgn0001319	FBgn0010355	FBgn0004859	FBgn0005511
FBgn0034821	FBgn0011640	FBgn0003720	FBgn0004863	FBgn0004106	FBgn0011737
FBgn0041171	FBgn0001219	FBgn0001202	FBgn0024728	FBgn0003892	FBgn0020309

Table C.2. Protein-protein interactions in Hedgehog signaling network in *D. melanogaster*-continued

Interactor A	**Interactor B**	**Interactor A**	**Interactor B**	**Interactor A**	**Interactor B**
FBgn0039170	FBgn0026192	FBgn0027548	FBgn0001990	FBgn0034904	FBgn0259217
FBgn0010280	FBgn0037555	FBgn0003870	FBgn0008649	FBgn0000166	FBgn0024491
FBgn0046874	FBgn0023531	FBgn0019809	FBgn0004598	FBgn0004647	FBgn0003870
FBgn0260632	FBgn0053980	FBgn0035938	FBgn0000439	FBgn0085448	FBgn0000529
FBgn0003892	FBgn0052486	FBgn0028577	FBgn0259794	FBgn0002633	FBgn0011277
FBgn0086364	FBgn0037094	FBgn0000163	FBgn0022131	FBgn0000117	FBgn0015624
FBgn0035993	FBgn0005630	FBgn0001139	FBgn0010575	FBgn0019650	FBgn0016917
FBgn0000499	FBgn0013591	FBgn0022238	FBgn0003870	FBgn0086358	FBgn0000157
FBgn0086384	FBgn0003345	FBgn0010235	FBgn0025334	FBgn0002973	FBgn0022131
FBgn0003031	FBgn0020496	FBgn0039044	FBgn0003479	FBgn0000588	FBgn0000629
FBgn0003410	FBgn0003870	FBgn0031450	FBgn0000658	FBgn0004647	FBgn0015778
FBgn0086384	FBgn0087002	FBgn0002609	FBgn0002631	FBgn0000499	FBgn0003090
FBgn0010379	FBgn0003479	FBgn0001990	FBgn0001990	FBgn0000529	FBgn0004863
FBgn0041582	FBgn0001235	FBgn0000233	FBgn0011836	FBgn0003334	FBgn0004861
FBgn0004896	FBgn0250848	FBgn0038063	FBgn0023215	FBgn0000352	FBgn0000273
FBgn0086384	FBgn0038418	FBgn0002633	FBgn0000964	FBgn0041582	FBgn0041582
FBgn0003460	FBgn0039038	FBgn0003415	FBgn0015618	FBgn0039907	FBgn0043900
FBgn0015624	FBgn0042630	FBgn0004595	FBgn0010300	FBgn0010235	FBgn0085386
FBgn0259220	FBgn0025334	FBgn0000117	FBgn0003944	FBgn0003964	FBgn0023518
FBgn0027356	FBgn0259174	FBgn0001168	FBgn0020496	FBgn0010379	FBgn0019650
FBgn0011648	FBgn0004893	FBgn0259220	FBgn0259220	FBgn0025638	FBgn0032956
FBgn0001078	FBgn0004907	FBgn0013765	FBgn0002873	FBgn0003371	FBgn0000117
FBgn0003326	FBgn0004647	FBgn0011276	FBgn0010602	FBgn0000022	FBgn0002735
FBgn0010379	FBgn0016081	FBgn0002413	FBgn0003068	FBgn0003430	FBgn0011640
FBgn0003124	FBgn0003270	FBgn0023522	FBgn0003380	FBgn0259794	FBgn0053169
FBgn0024330	FBgn0017578	FBgn0000439	FBgn0000611	FBgn0004638	FBgn0016794
FBgn0004638	FBgn0036274	FBgn0015282	FBgn0036224	FBgn0001978	FBgn0019650
FBgn0000097	FBgn0023214	FBgn0000413	FBgn0002733	FBgn0001150	FBgn0005630
FBgn0005355	FBgn0032475	FBgn0000413	FBgn0002735	FBgn0027788	FBgn0004598
FBgn0020496	FBgn0001320	FBgn0026411	FBgn0037672	FBgn0000042	FBgn0087008
FBgn0000163	FBgn0026192	FBgn0000459	FBgn0020496	FBgn0004647	FBgn0023215
FBgn0086384	FBgn0000250	FBgn0035956	FBgn0004863	FBgn0000022	FBgn0002733
FBgn0004861	FBgn0013263	FBgn0001319	FBgn0039283	FBgn0025680	FBgn0004102
FBgn0001323	FBgn0053980	FBgn0010235	FBgn0015014	FBgn0003460	FBgn0259750
FBgn0020496	FBgn0001325	FBgn0031878	FBgn0000611	FBgn0025458	FBgn0001994
FBgn0010315	FBgn0000166	FBgn0003892	FBgn0011606	FBgn0004510	FBgn0013725
FBgn0022131	FBgn0024250	FBgn0026170	FBgn0010602	FBgn0001168	FBgn0010109
FBgn0024371	FBgn0011763	FBgn0008646	FBgn0000490	FBgn0004858	FBgn0000258
FBgn0003986	FBgn0000182	FBgn0039044	FBgn0039923	FBgn0003479	FBgn0053208
FBgn0025637	FBgn0023423	FBgn0000182	FBgn0001120	FBgn0038747	FBgn0039066
FBgn0035424	FBgn0000042	FBgn0011737	FBgn0010602	FBgn0000591	FBgn0000591
FBgn0011661	FBgn0010110	FBgn0010379	FBgn0000546	FBgn0013765	FBgn0000524
FBgn0010315	FBgn0000546	FBgn0002733	FBgn0015550	FBgn0036671	FBgn0013765
FBgn0000114	FBgn0004882	FBgn0027052	FBgn0000250	FBgn0003600	FBgn0003607
FBgn0003892	FBgn0250786	FBgn0001319	FBgn0003870	FBgn0004859	FBgn0005355
FBgn0000229	FBgn0011737	FBgn0011771	FBgn0001990	FBgn0003870	FBgn0023444
FBgn0014396	FBgn0010355	FBgn0024191	FBgn0036274	FBgn0026598	FBgn0000117
FBgn0005355	FBgn0003862	FBgn0024191	FBgn0020369	FBgn0027788	FBgn0000524
FBgn0032956	FBgn0023091	FBgn0025638	FBgn0024250	FBgn0014931	FBgn0014931
FBgn0013765	FBgn0259794	FBgn0019809	FBgn0011260	FBgn0259220	FBgn0003479
FBgn0024321	FBgn0020496	FBgn0002631	FBgn0015550	FBgn0000250	FBgn0260632
FBgn0000414	FBgn0003366	FBgn0038852	FBgn0015904	FBgn0000352	FBgn0015396
FBgn0002631	FBgn0002733	FBgn0003002	FBgn0259794	FBgn0000212	FBgn0004050
FBgn0002631	FBgn0002734	FBgn0086358	FBgn0000114	FBgn0013984	FBgn0013984

Table C.2. Protein-protein interactions in Hedgehog signaling network in *D. melanogaster*-continued

Interactor A	**Interactor B**	**Interactor A**	**Interactor B**	**Interactor A**	**Interactor B**
FBgn0002631	FBgn0002735	FBgn0086358	FBgn0026323	FBgn0014396	FBgn0000179
FBgn0000611	FBgn0001235	FBgn0000629	FBgn0020887	FBgn0000382	FBgn0016794
FBgn0000229	FBgn0086358	FBgn0004859	FBgn0000179	FBgn0000137	FBgn0002609
FBgn0025458	FBgn0005630	FBgn0000964	FBgn0034802	FBgn0002941	FBgn0259794
FBgn0010379	FBgn0038197	FBgn0041582	FBgn0013725	FBgn0025637	FBgn0041171
FBgn0032202	FBgn0039209	FBgn0013725	FBgn0004907	FBgn0004859	FBgn0000242
FBgn0015805	FBgn0020887	FBgn0085448	FBgn0015903	FBgn0015624	FBgn0000157
FBgn0001170	FBgn0037094	FBgn0024330	FBgn0022740	FBgn0001150	FBgn0032202
FBgn0000529	FBgn0002940	FBgn0035938	FBgn0023091	FBgn0259794	FBgn0013725
FBgn0003124	FBgn0028789	FBgn0010315	FBgn0023091	FBgn0003002	FBgn0025334
FBgn0001170	FBgn0001139	FBgn0038852	FBgn0004863	FBgn0013725	FBgn0013725
FBgn0023215	FBgn0017578	FBgn0019686	FBgn0259220	FBgn0004896	FBgn0038271
FBgn0001139	FBgn0020496	FBgn0086364	FBgn0035849	FBgn0002733	FBgn0010433
FBgn0001319	FBgn0024510	FBgn0000472	FBgn0041171	FBgn0025458	FBgn0086384
FBgn0011661	FBgn0040232	FBgn0260632	FBgn0003942	FBgn0004837	FBgn0010110
FBgn0000964	FBgn0000964	FBgn0010441	FBgn0260632	FBgn0031450	FBgn0027356
FBgn0001139	FBgn0002609	FBgn0002973	FBgn0026192	FBgn0013725	FBgn0023444
FBgn0000061	FBgn0003944	FBgn0000546	FBgn0023518	FBgn0001319	FBgn0003270
FBgn0029905	FBgn0000042	FBgn0000166	FBgn0003870	FBgn0004915	FBgn0022740
FBgn0004859	FBgn0015624	FBgn0002734	FBgn0020496	FBgn0024222	FBgn0024222
FBgn0086384	FBgn0036349	FBgn0003862	FBgn0003862	FBgn0000163	FBgn0002973
FBgn0019650	FBgn0250788	FBgn0000463	FBgn0086442	FBgn0025632	FBgn0000042
FBgn0086358	FBgn0025334	FBgn0024191	FBgn0000183	FBgn0000114	FBgn0015903
FBgn0000629	FBgn0024491	FBgn0052105	FBgn0027338	FBgn0041171	FBgn0000490
FBgn0000588	FBgn0000588	FBgn0000617	FBgn0037555	FBgn0260632	FBgn0001990
FBgn0001981	FBgn0013765	FBgn0003042	FBgn0015805	FBgn0028685	FBgn0028687
FBgn0001139	FBgn0026192	FBgn0000163	FBgn0026319	FBgn0024222	FBgn0041205
FBgn0003944	FBgn0015903	FBgn0015778	FBgn0014931	FBgn0028685	FBgn0028685
FBgn0000591	FBgn0002631	FBgn0024371	FBgn0000611	FBgn0003479	FBgn0039923
FBgn0001170	FBgn0046874	FBgn0003023	FBgn0003944	FBgn0013725	FBgn0003410
FBgn0029905	FBgn0016917	FBgn0000259	FBgn0000258	FBgn0004647	FBgn0031450
FBgn0000591	FBgn0002633	FBgn0030695	FBgn0030695	FBgn0000352	FBgn0004859
FBgn0003479	FBgn0003612	FBgn0001078	FBgn0000411	FBgn0086384	FBgn0051792
FBgn0004859	FBgn0003415	FBgn0003068	FBgn0014396	FBgn0041582	FBgn0024250
FBgn0000611	FBgn0003339	FBgn0004859	FBgn0004859	FBgn0003475	FBgn0003317
FBgn0053520	FBgn0000346	FBgn0020369	FBgn0015282	FBgn0000499	FBgn0002945
FBgn0032492	FBgn0015282	FBgn0004859	FBgn0004858	FBgn0002609	FBgn0004170
FBgn0025637	FBgn0021875	FBgn0003118	FBgn0003256	FBgn0000210	FBgn0046874
FBgn0000463	FBgn0004647	FBgn0036497	FBgn0027052	FBgn0004859	FBgn0005771
FBgn0039044	FBgn0033636	FBgn0086384	FBgn0259234	FBgn0000273	FBgn0004859
FBgn0000392	FBgn0001219	FBgn0000413	FBgn0000575	FBgn0028577	FBgn0000042
FBgn0003941	FBgn0003942	FBgn0000560	FBgn0002631	FBgn0000499	FBgn0052532
FBgn0052486	FBgn0005694	FBgn0003124	FBgn0036799	FBgn0003124	FBgn0042650
FBgn0023091	FBgn0052486	FBgn0036671	FBgn0020510	FBgn0000629	FBgn0015805

APPENDIX D: DEGREE DISTRIBUTION OF THE PROTEINS IN THE NETWORKS

Table D.1. Degree distribution of the proteins in the reconstructed Wnt/β-catenin network

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0004859	ci	38	FBgn0024250	brk	10	FBgn0032956	Cul-2	7
FBgn0086384	Mer	36	FBgn0000463	Dl	10	FBgn0036274	CG4328	7
FBgn0003892	ptc	27	FBgn0041171	ago	10	FBgn0015778	rin	7
FBgn0001139	gro	22	FBgn0259220	Doa	10	FBgn0005771	noc	7
FBgn0020496	CtBP	20	FBgn0000524	dx	10	FBgn0023215	Mnt	7
FBgn0024371	E2f2	19	FBgn0000250	cact	10	FBgn0085432	pan	7
FBgn0011661	Moe	19	FBgn0002734	HLHmdelta	10	FBgn0029711	Usf	6
FBgn0011715	Snr1	17	FBgn0026192	par-6	10	FBgn0000504	dsx	6
FBgn0003870	ttk	17	FBgn0003460	so	9	FBgn0042630	Sox21b	6
FBgn0259794	sinah	17	FBgn0051999	CG31999	9	FBgn0011763	Dp	6
FBgn0003479	spn-A	16	FBgn0015624	nej	9	FBgn0038271	CG3731	6
FBgn0004647	N	16	FBgn0027788	Hey	9	FBgn0003345	sd	6
FBgn0002733	HLHmbeta	16	FBgn0000259	CkIIbeta	9	FBgn0087008	e(y)3	6
FBgn0260632	dl	16	FBgn0001079	fu	9	FBgn0053520	Rpb4	6
FBgn0019650	toy	16	FBgn0000964	tj	9	FBgn0086758	chinmo	6
FBgn0025637	skpA	15	FBgn0004907	14-3-3zeta	9	FBgn0027052	CHIP	6
FBgn0002633	HLHm7	15	FBgn0025334	PHDP	9	FBgn0038578	MED17	6
FBgn0003464	sol	14	FBgn0013263	Trl	8	FBgn0004638	drk	6
FBgn0031850	Tsp	14	FBgn0001219	Hsc70-4	8	FBgn0003942	RpS27A	6
FBgn0026262	bip2	14	FBgn0001168	h	8	FBgn0037555	Ada2b	6
FBgn0003944	Ubx	14	FBgn0000578	ena	8	FBgn0003013	osa	6
FBgn0003124	polo	14	FBgn0025806	Rap2l	8	FBgn0028902	Tektin-A	6
FBgn0041582	tamo	14	FBgn0001170	H2.0	8	FBgn0001291	Jra	6
FBgn0000042	Act5C	14	FBgn0000588	esc	8	FBgn0003002	opa	6
FBgn0013765	cnn	14	FBgn0023091	dimm	8	FBgn0015589	Apc	6
FBgn0000117	arm	14	FBgn0003044	Pcl	8	FBgn0026313	X11L	6
FBgn0003410	sina	13	FBgn0000258	CkIIalpha	8	FBgn0000319	Chc	6
FBgn0031450	Hrs	13	FBgn0010333	Rac1	8	FBgn0002781	mod(mdg4)	6
FBgn0002735	HLHmgamma	13	FBgn0028734	Fmr1	8	FBgn0010109	dpn	6
FBgn0002631	HLHm5	13	FBgn0005630	lola	8	FBgn0010355	Taf1	6
FBgn0000166	bcd	13	FBgn0000629	E(z)	8	FBgn0015286	Rala	6
FBgn0013725	phyl	13	FBgn0040078	pont	7	FBgn0035849	ERR	6
FBgn0011648	Mad	12	FBgn0035357	MEP-1	7	FBgn0000283	Cp190	6
FBgn0000413	da	12	FBgn0015805	Rpd3	7	FBgn0002914	Myb	6
FBgn0002609	HLHm3	12	FBgn0015903	apt	7	FBgn0035993	Nf-YA	6
FBgn0000499	dsh	12	FBgn0001990	wek	7	FBgn0004170	sc	6
FBgn0001319	kn	12	FBgn0024491	Bin1	7	FBgn0039283	danr	6
FBgn0040080	raps	11	FBgn0000546	EcR	7	FBgn0053208	Mical	6
FBgn0004863	C15	11	FBgn0000212	brm	7	FBgn0028685	Rpt4	6
FBgn0011277	HLH4C	11	FBgn0053980	Vsx2	7	FBgn0015542	sima	5
FBgn0031537	sec5	11	FBgn0028577	pUf68	7	FBgn0004896	fd59A	5
FBgn0010379	Akt1	11	FBgn0000352	cos	7	FBgn0001235	hth	5
FBgn0039044	p53	11	FBgn0010315	CycD	7	FBgn0016797	fz2	5
FBgn0086358	Tab2	11	FBgn0000611	exd	7	FBgn0022131	aPKC	5
FBgn0000591	E(spl)	11	FBgn0020369	Pros45	7	FBgn0008646	E5	5

Table D.1. Degree distribution of the proteins in the reconstructed Wnt/β-catenin network-continued

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0034904	CG15800	5	FBgn0003371	sgg	4	FBgn0002985	odd	4
FBgn0015509	lin19	5	FBgn0250785	vari	4	FBgn0003366	sev	3
FBgn0001323	knrl	5	FBgn0004858	elB	4	FBgn0004595	pros	3
FBgn0023509	mip130	5	FBgn0015602	BEAF-32	4	FBgn0004598	Fur2	3
FBgn0023444	ebi	5	FBgn0001120	gnu	4	FBgn0001942	eIF-4a	3
FBgn0004837	Su(H)	5	FBgn0038852	CG7056	4	FBgn0001233	Hsp83	3
FBgn0008651	lbl	5	FBgn0001133	grau	4	FBgn0031878	sip2	3
FBgn0066101	LpR1	5	FBgn0038035	lig3	4	FBgn0003475	spir	3
FBgn0023423	slmb	5	FBgn0001150	gt	4	FBgn0011766	E2f	3
FBgn0003567	su(Hw)	5	FBgn0000575	emc	4	FBgn0250788	beta-Spec	3
FBgn0011586	e(r)	5	FBgn0004510	Ets97D	4	FBgn0067864	Patj	3
FBgn0038747	RhoGAP92B	5	FBgn0011260	Sema-2a	4	FBgn0004870	bab1	3
FBgn0025743	mbt	5	FBgn0024728	Slip1	4	FBgn0013984	InR	3
FBgn0000330	cm	5	FBgn0011300	babo	4	FBgn0001269	inv	3
FBgn0026318	Traf6	5	FBgn0011737	wee	4	FBgn0015609	CadN	3
FBgn0001981	esg	5	FBgn0000338	cnc	4	FBgn0023172	RhoGEF2	3
FBgn0032515	loqs	5	FBgn0024222	ird5	4	FBgn0001320	kni	3
FBgn0003256	rl	5	FBgn0010280	Taf4	4	FBgn0001324	kto	3
FBgn0011640	lark	5	FBgn0011290	Taf12	4	FBgn0001122	G-oalpha47A	3
FBgn0000229	bsk	5	FBgn0001978	stc	4	FBgn0015014	tgo	3
FBgn0024330	MED6	5	FBgn0003448	sna	4	FBgn0085369	CG34340	3
FBgn0000529	bsh	5	FBgn0039016	Dcr-1	4	FBgn0004861	ph-p	3
FBgn0014396	tim	5	FBgn0001085	fz	4	FBgn0015904	ara	3
FBgn0014931	CG2678	5	FBgn0026562	BM-40-SPARC	4	FBgn0038576	Arp5	3
FBgn0026411	Lim1	5	FBgn0036224	Rpt4R	4	FBgn0022382	Pka-R2	3
FBgn0015282	Pros26.4	5	FBgn0010342	Map60	4	FBgn0053519	Unc-89	3
FBgn0002921	Atpalpha	5	FBgn0033636	tou	4	FBgn0019809	gcm2	3
FBgn0000472	dm	5	FBgn0030318	rho-4	4	FBgn0039585	CG1894	3
FBgn0001078	ftz-f1	5	FBgn0005631	robo	4	FBgn0029905	Nf-YC	3
FBgn0086364	rdx	5	FBgn0000392	cup	4	FBgn0003270	amos	3
FBgn0010323	Gsc	5	FBgn0027356	Amph	4	FBgn0002413	dco	3
FBgn0046874	Pif1B	5	FBgn0000179	bi	4	FBgn0020503	CLIP-190	3
FBgn0000617	e(y)1	5	FBgn0005558	ey	4	FBgn0000439	Dfd	3
FBgn0002023	Lim3	5	FBgn0026170	smt3	4	FBgn0025800	Smox	3
FBgn0022238	lolal	5	FBgn0000182	BicC	4	FBgn0000577	en	3
FBgn0052486	CG32486	5	FBgn0000163	baz	4	FBgn0003941	RpL40	3
FBgn0002940	ninaE	5	FBgn0028642	esn	4	FBgn0259481	Mob2	3
FBgn0000137	ase	5	FBgn0013718	nuf	4	FBgn0053967	CG33967	3
FBgn0000114	aret	5	FBgn0022720	zf30C	4	FBgn0004050	z	3
FBgn0026056	Rlip	5	FBgn0025458	BubR1	4	FBgn0010825	Gug	3
FBgn0026597	Axn	5	FBgn0243505	sdt	4	FBgn0024732	Drep-1	3
FBgn0015799	Rbf	5	FBgn0020887	Su(z)12	4	FBgn0011817	nmo	3
FBgn0002973	numb	5	FBgn0259217	Csk	4	FBgn0021760	chb	3
FBgn0005355	Su(fu)	5	FBgn0038390	Rbf2	4	FBgn0000560	eg	3
FBgn0015550	tap	4	FBgn0000022	ac	4	FBgn0003145	prd	3

Table D.1. Degree distribution of the proteins in the reconstructed Wnt/β-catenin network-continued

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0025638	Roc1a	3	FBgn0035638	Tektin-C	3	FBgn0003687	Tbp	2
FBgn0003415	skd	3	FBgn0028687	Rpt1	3	FBgn0011276	HLH3B	2
FBgn0003429	slo	3	FBgn0011771	Hem	2	FBgn0024234	gbb	2
FBgn0003334	Scm	3	FBgn0004895	fd64A	2	FBgn0036671	CG9951	2
FBgn0039907	lgs	3	FBgn0050420	Atf-2	2	FBgn0015331	abs	2
FBgn0003717	Tl	3	FBgn0004893	bowl	2	FBgn0025741	plexA	2
FBgn0003430	slp1	3	FBgn0000108	Appl	2	FBgn0003425	sli	2
FBgn0036697	rogdi	3	FBgn0033483	egr	2	FBgn0024321	NK7.1	2
FBgn0003129	Poxm	3	FBgn0013983	imd	2	FBgn0003031	pAbp	2
FBgn0003300	run	3	FBgn0250789	alpha-Spec	2	FBgn0010287	Trf	2
FBgn0032202	CG18619	3	FBgn0001202	hk	2	FBgn0026319	Traf4	2
FBgn0010194	Wnt5	3	FBgn0016794	dos	2	FBgn0011291	Taf11	2
FBgn0015371	chn	3	FBgn0003495	spz	2	FBgn0030600	hiw	2
FBgn0003896	tup	3	FBgn0004882	orb	2	FBgn0000547	ed	2
FBgn0037981	Spt3	3	FBgn0013997	Nrx-IV	2	FBgn0028386	cic	2
FBgn0000382	csw	3	FBgn0004606	zfh1	2	FBgn0003444	smo	2
FBgn0001624	dlg1	3	FBgn0023518	trr	2	FBgn0039209	CG13624	2
FBgn0039946	ATbp	3	FBgn0087002	Rfabg	2	FBgn0003118	pnt	2
FBgn0004106	cdc2	3	FBgn0004652	fru	2	FBgn0003720	tll	2
FBgn0030695	PGRP-LE	3	FBgn0016081	fry	2	FBgn0000411	D	2
FBgn0050011	gem	3	FBgn0008649	dei	2	FBgn0003053	peb	2
FBgn0039923	MED26	3	FBgn0024291	Sir2	2	FBgn0000414	Dab	2
FBgn0000253	Cam	3	FBgn0015618	Cdk8	2	FBgn0039601	CG1523	2
FBgn0003862	trx	3	FBgn0038063	Octbeta2R	2	FBgn0011747	Ank	2
FBgn0003607	Su(var)205	3	FBgn0013591	Mi-2	2	FBgn0039509	bigmax	2
FBgn0039936	CG11148	3	FBgn0053531	Ddr	2	FBgn0001965	Sos	2
FBgn0016917	Stat92E	3	FBgn0052532	CG32532	2	FBgn0003317	sax	2
FBgn0017578	Max	3	FBgn0086680	vvl	2	FBgn0003511	Sry-beta	2
FBgn0017453	Zn72D	3	FBgn0001148	gsb	2	FBgn0000242	Bx	2
FBgn0003090	pk	3	FBgn0032872	CG2478	2	FBgn0001090	bnb	2
FBgn0004009	wg	3	FBgn0023531	CG32809	2	FBgn0025680	cry	2
FBgn0260635	th	3	FBgn0259174	Nedd4	2	FBgn0004102	oc	2
FBgn0010110	east	3	FBgn0003380	Sh	2	FBgn0000233	btd	2
FBgn0003068	per	3	FBgn0032475	Sfmbt	2	FBgn0010380	Bap	2
FBgn0028407	Drep-3	3	FBgn0038046	CG5641	2	FBgn0028550	A3-3	2
FBgn0000490	dpp	3	FBgn0004644	hh	2	FBgn0259750	ab	2
FBgn0000625	eyg	3	FBgn0023522	CG11596	2	FBgn0030242	sofe	2
FBgn0013750	Arf51F	3	FBgn0030941	wgn	2	FBgn0000996	dup	2
FBgn0085448	Hmx	3	FBgn0061173	fd3F	2	FBgn0036134	Mnf	2
FBgn0010433	ato	3	FBgn0016977	spen	2	FBgn0033081	geminin	2
FBgn0004915	TfIIB	3	FBgn0001169	H	2	FBgn0033073	bin3	2
FBgn0022740	HLH54F	3	FBgn0051619	CG31619	2	FBgn0026611	AGO1	2
FBgn0000157	Dll	3	FBgn0003943	Ubi-p63E	2	FBgn0036558	mib1	2
FBgn0002932	neur	3	FBgn0030749	Anxb11	2	FBgn0003861	trp	2
FBgn0020386	Pk61C	3	FBgn0004053	zen	2	FBgn0000251	cad	2

Table D.1. Degree distribution of the proteins in the reconstructed Wnt/β-catenin network-continued

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0003600	Su(var)3-9	2	FBgn0036497	ran-like	2	FBgn0001325	Kr	1
FBgn0259785	pzg	2	FBgn0004167	kst	2	FBgn0038197	foxo	1
FBgn0037093	CG7597	2	FBgn0020381	Dredd	2	FBgn0027950	MBD-like	1
FBgn0035976	PGRP-LC	2	FBgn0028789	Doc1	2	FBgn0004666	sim	1
FBgn0037094	CG7611	2	FBgn0039788	Rpt6R	2	FBgn0086655	jing	1
FBgn0024510	dlt	2	FBgn0020493	Dad	2	FBgn0038439	Cad89D	1
FBgn0003986	vnd	2	FBgn0023388	Dap160	2	FBgn0004583	ex	1
FBgn0010341	Cdc42	2	FBgn0032105	borr	2	FBgn0003382	sha	1
FBgn0086902	kis	2	FBgn0000140	asp	2	FBgn0259176	bun	1
FBgn0000658	fj	2	FBgn0260934	par-1	2	FBgn0015907	bl	1
FBgn0000273	Pka-C1	2	FBgn0013531	MED20	2	FBgn0004435	Galpha49B	1
FBgn0002922	nau	2	FBgn0000119	arr	2	FBgn0041205	key	1
FBgn0026404	Nc	2	FBgn0036254	CG5645	2	FBgn0004649	yl	1
FBgn0035769	CTCF	2	FBgn0015790	Rab11	2	FBgn0015024	Cklalpha	1
FBgn0029687	Vap-33-1	2	FBgn0002873	mud	2	FBgn0003391	shg	1
FBgn0086910	l(3)neo38	2	FBgn0033998	row	2	FBgn0037672	sage	1
FBgn0001077	ftz	2	FBgn0023214	edl	2	FBgn0034400	CG15099	1
FBgn0002121	l(2)gl	2	FBgn0000028	acj6	2	FBgn0011836	Taf2	1
FBgn0010215	alpha-Cat	2	FBgn0026369	Sara	1	FBgn0037466	CG1965	1
FBgn0030018	slpr	2	FBgn0001222	Hsf	1	FBgn0036661	CG9705	1
FBgn0028408	Drep-2	2	FBgn0015240	Hr96	1	FBgn0038418	pad	1
FBgn0033029	l(2)NC136	2	FBgn0016034	mael	1	FBgn0037377	CG1218	1
FBgn0039066	EloA	2	FBgn0031872	iHog	1	FBgn0003169	put	1
FBgn0259685	crb	2	FBgn0031871	CG10158	1	FBgn0011577	dally	1
FBgn0000635	Fas2	2	FBgn0029708	CG3556	1	FBgn0036799	CG13380	1
FBgn0011225	jar	2	FBgn0004624	CaMKII	1	FBgn0037475	Fer1	1
FBgn0010417	Taf6	2	FBgn0004878	cas	1	FBgn0034534	maf-S	1
FBgn0040466	Dip2	2	FBgn0250786	Chd1	1	FBgn0000448	Hr46	1
FBgn0038341	CG14869	2	FBgn0001105	Gbeta13F	1	FBgn0086711	mol	1
FBgn0013753	Bgb	2	FBgn0027066	Eb1	1	FBgn0044323	Cka	1
FBgn0052392	CG32392	2	FBgn0011606	Klp3A	1	FBgn0011259	Sema-1a	1
FBgn0013755	Bro	2	FBgn0031985	CG8683	1	FBgn0017581	Lk6	1
FBgn0013759	Caki	2	FBgn0022959	yps	1	FBgn0033015	d4	1
FBgn0039286	dan	2	FBgn0003205	Ras85D	1	FBgn0020621	Pkn	1
FBgn0042650	disco-r	2	FBgn0019947	Psn	1	FBgn0037937	Fer3	1
FBgn0085445	Ank2	2	FBgn0004603	Src42A	1	FBgn0004049	yrt	1
FBgn0000721	for	2	FBgn0031851	CG11188	1	FBgn0037751	topi	1
FBgn0026175	skpC	2	FBgn0004607	zfh2	1	FBgn0024245	dnt	1
FBgn0019686	lok	2	FBgn0026263	bip1	1	FBgn0000459	disco	1
FBgn0038928	BG4	2	FBgn0053936	CG33936	1	FBgn0003964	usp	1
FBgn0002968	Nrg	2	FBgn0040372	G9a	1	FBgn0001297	kay	1
FBgn0000046	Act87E	2	FBgn0032467	CG9934	1	FBgn0003557	Su(dx)	1
FBgn0085451	CG34422	2	FBgn0004856	Bx42	1	FBgn0086442	mib2	1
FBgn0000606	eve	2	FBgn0004364	18w	1	FBgn0011274	Dif	1
FBgn0020379	Rfx	2	FBgn0024909	Taf7	1	FBgn0025632	CG4313	1

Table D.1. Degree distribution of the proteins in the reconstructed Wnt/β-catenin network-continued

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0040918	Lag1	1	FBgn0003749	trh	1	FBgn0030151	CG1354	1
FBgn0024184	unc-4	1	FBgn0039038	CG6688	1	FBgn0035956	Doc2	1
FBgn0003975	vg	1	FBgn0003612	Su(var)2-10	1	FBgn0035954	Doc3	1
FBgn0024846	p38b	1	FBgn0020309	crol	1	FBgn0035021	CG4622	1
FBgn0025740	plexB	1	FBgn0020306	dom	1	FBgn0052280	CG32280	1
FBgn0038659	endoA	1	FBgn0014143	croc	1	FBgn0002945	nkd	1
FBgn0001994	crp	1	FBgn0037811	CG12592	1	FBgn0002941	slou	1
FBgn0024194	rasp	1	FBgn0011481	Ssdp	1	FBgn0034802	CG3800	1
FBgn0003900	twi	1	FBgn0039938	Sox102F	1	FBgn0010452	trn	1
FBgn0003520	stau	1	FBgn0002521	pho	1	FBgn0000061	al	1
FBgn0026323	Tak1	1	FBgn0029114	Tollo	1	FBgn0005596	yemalpha	1
FBgn0015380	drl	1	FBgn0035975	PGRP-LA	1	FBgn0005694	Aef1	1
FBgn0003326	sca	1	FBgn0000289	cg	1	FBgn0026577	CG8677	1
FBgn0003328	scb	1	FBgn0005511	mid	1	FBgn0028999	nerfin-1	1
FBgn0011674	insc	1	FBgn0028926	NC2beta	1	FBgn0035150	Rev1	1
FBgn0000206	boss	1	FBgn0011202	dia	1	FBgn0026080	Tip60	1
FBgn0011725	twin	1	FBgn0027574	CG5815	1	FBgn0000008	a	1
FBgn0024836	stan	1	FBgn0026401	Nipped-B	1	FBgn0085410	CG34381	1
FBgn0003716	tkv	1	FBgn0000659	fkh	1	FBgn0034160	CG5550	1
FBgn0000346	comt	1	FBgn0020224	Cbl	1	FBgn0004197	Ser	1
FBgn0015396	jumu	1	FBgn0029105	alpha-catenin-related	1	FBgn0027609	morgue	1
FBgn0003339	Scr	1	FBgn0037734	trbd	1	FBgn0000017	Abl	1
FBgn0003502	Btk29A	1	FBgn0010349	Dhc64C	1	FBgn0026598	Apc2	1
FBgn0030899	Her	1	FBgn0000097	aop	1	FBgn0004394	pdm2	1
FBgn0003254	rib	1	FBgn0011236	ken	1	FBgn0035518	CG15011	1
FBgn0015567	alpha-Adaptin	1	FBgn0039170	CG13609	1	FBgn0052343	CG32343	1
FBgn0026208	mbf1	1	FBgn0027343	fz3	1			
FBgn0002774	mle	1	FBgn0001075	ft	1			
FBgn0000210	br	1	FBgn0052133	ptip	1			
FBgn0003512	Sry-delta	1	FBgn0035989	CG3967	1			
FBgn0021875	Zfrp8	1	FBgn0053169	CG33169	1			
FBgn0021873	Gef26	1	FBgn0025525	bab2	1			
FBgn0259234	Camta	1	FBgn0032940	Mio	1			
FBgn0011655	Med	1	FBgn0038206	twf	1			
FBgn0002780	mod	1	FBgn0020255	ran	1			
FBgn0003651	svp	1	FBgn0010441	pll	1			
FBgn0043900	pygo	1	FBgn0010300	brat	1			
FBgn0028369	kirre	1	FBgn0010434	cora	1			
FBgn0014010	Rab5	1	FBgn0000810	fs(1)K10	1			
FBgn0014011	Rac2	1	FBgn0010575	sbb	1			
FBgn0034476	Toll-7	1	FBgn0041094	scyl	1			
FBgn0028852	CG15262	1	FBgn0034926	CG5591	1			
FBgn0025681	CG3558	1	FBgn0034821	CG9876	1			
FBgn0029006	lack	1	FBgn0004914	Hnf4	1			
FBgn0000370	crc	1	FBgn0052475	mthl8	1			

Table D.2. Degree distribution of the proteins in the reconstructed Hedgehog network

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0004859	ci	39	FBgn0000499	dsh	9	FBgn0001308	Khc	6
FBgn0086384	Mer	30	FBgn0000964	tj	9	FBgn0013718	nuf	6
FBgn0003892	ptc	28	FBgn0015624	nej	8	FBgn0000117	arm	6
FBgn0001139	gro	21	FBgn0001168	h	8	FBgn0028685	Rpt4	6
FBgn0020496	CtBP	19	FBgn0024250	brk	8	FBgn0003371	sgg	5
FBgn0011661	Moe	17	FBgn0001990	wek	8	FBgn0042630	Sox21b	5
FBgn0003870	ttk	16	FBgn0011648	Mad	8	FBgn0022131	aPKC	5
FBgn0002733	HLHmbeta	16	FBgn0010235	Klc	8	FBgn0008646	E5	5
FBgn0259794	sinah	16	FBgn0000258	CkIIalpha	8	FBgn0023444	ebi	5
FBgn0260632	dl	16	FBgn0028734	Fmr1	8	FBgn0015805	Rpd3	5
FBgn0002633	HLHm7	15	FBgn0001079	fu	8	FBgn0038747	RhoGAP92B	5
FBgn0019650	toy	15	FBgn0000611	exd	8	FBgn0001291	Jra	5
FBgn0003479	spn-A	14	FBgn0020369	Pros45	8	FBgn0003002	opa	5
FBgn0004647	N	14	FBgn0036274	CG4328	8	FBgn0000338	cnc	5
FBgn0041582	tamo	14	FBgn0003460	so	7	FBgn0003444	smo	5
FBgn0010602	lwr	14	FBgn0013263	Trl	7	FBgn0000229	bsk	5
FBgn0013765	cnn	14	FBgn0001219	Hsc70-4	7	FBgn0000529	bsh	5
FBgn0025637	skpA	13	FBgn0000463	Dl	7	FBgn0027338	Kap-alpha3	5
FBgn0024371	E2f2	13	FBgn0041171	ago	7	FBgn0026411	Lim1	5
FBgn0003124	polo	13	FBgn0024191	sip1	7	FBgn0000273	Pka-C1	5
FBgn0002735	HLHmgamma	13	FBgn0024491	Bin1	7	FBgn0035993	Nf-YA	5
FBgn0002631	HLHm5	13	FBgn0000546	EcR	7	FBgn0001078	ftz-f1	5
FBgn0001319	kn	13	FBgn0000524	dx	7	FBgn0010315	CycD	5
FBgn0003464	sol	12	FBgn0028577	pUf68	7	FBgn0010323	Gsc	5
FBgn0000413	da	12	FBgn0015282	Pros26.4	7	FBgn0046874	Pif1B	5
FBgn0002609	HLHm3	12	FBgn0005630	lola	7	FBgn0039283	danr	5
FBgn0000166	bcd	12	FBgn0000629	E(z)	7	FBgn0035938	orb2	5
FBgn0003944	Ubx	11	FBgn0004907	14-3-3zeta	7	FBgn0000182	BicC	5
FBgn0259220	Doa	11	FBgn0005771	noc	7	FBgn0002023	Lim3	5
FBgn0000250	cact	11	FBgn0023215	Mnt	7	FBgn0052486	CG32486	5
FBgn0000591	E(spl)	11	FBgn0004896	fd59A	6	FBgn0032956	Cul-2	5
FBgn0000042	Act5C	11	FBgn0038271	CG3731	6	FBgn0000137	ase	5
FBgn0013725	phyl	11	FBgn0053520	Rpb4	6	FBgn0022720	zf30C	5
FBgn0031450	Hrs	10	FBgn0027052	CHIP	6	FBgn0015778	rin	5
FBgn0010379	Akt1	10	FBgn0015903	apt	6	FBgn0053208	Mical	5
FBgn0002734	HLHmdelta	10	FBgn0023423	slmb	6	FBgn0000114	aret	5
FBgn0039044	p53	10	FBgn0003942	RpS27A	6	FBgn0002973	numb	5
FBgn0086358	Tab2	10	FBgn0027788	Hey	6	FBgn0005355	Su(fu)	5
FBgn0025334	PHDP	10	FBgn0000588	esc	6	FBgn0004598	Fur2	4
FBgn0004863	C15	9	FBgn0037555	Ada2b	6	FBgn0000504	dsx	4
FBgn0003410	sina	9	FBgn0010109	dpn	6	FBgn0001235	hth	4
FBgn0011277	HLH4C	9	FBgn0014931	CG2678	6	FBgn0003345	sd	4
FBgn0023091	dimm	9	FBgn0010355	Taf1	6	FBgn0015509	lin19	4
FBgn0000352	cos	9	FBgn0004170	sc	6	FBgn0004858	elB	4
FBgn0000259	CkIIbeta	9	FBgn0026192	par-6	6	FBgn0001323	knrl	4

Table D.2. Degree distribution of the proteins in the reconstructed Hedgehog network-continued

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0001120	gnu	4	FBgn0013984	InR	3	FBgn0003090	pk	3
FBgn0015014	tgo	4	FBgn0034904	CG15800	3	FBgn0033636	tou	3
FBgn0038852	CG7056	4	FBgn0087008	e(y)3	3	FBgn0010110	east	3
FBgn0004638	drk	4	FBgn0001320	kni	3	FBgn0003068	per	3
FBgn0004644	hh	4	FBgn0015602	BEAF-32	3	FBgn0005631	robo	3
FBgn0015024	CkIalpha	4	FBgn0001324	kto	3	FBgn0000392	cup	3
FBgn0029905	Nf-YC	4	FBgn0085369	CG34340	3	FBgn0000490	dpp	3
FBgn0000439	Dfd	4	FBgn0004861	ph-p	3	FBgn0019686	lok	3
FBgn0000575	emc	4	FBgn0004837	Su(H)	3	FBgn0010433	ato	3
FBgn0001170	H2.0	4	FBgn0015904	ara	3	FBgn0000617	e(y)1	3
FBgn0004510	Ets97D	4	FBgn0008651	lbl	3	FBgn0020887	Su(z)12	3
FBgn0025638	Roc1a	4	FBgn0019809	gcm2	3	FBgn0028687	Rpt1	3
FBgn0011737	wee	4	FBgn0001150	gt	3	FBgn0004895	fd64A	2
FBgn0024222	ird5	4	FBgn0003270	amos	3	FBgn0004893	bowl	2
FBgn0010280	Taf4	4	FBgn0002413	dco	3	FBgn0004595	pros	2
FBgn0001981	esg	4	FBgn0000577	en	3	FBgn0001233	Hsp83	2
FBgn0003256	rl	4	FBgn0053967	CG33967	3	FBgn0031878	sip2	2
FBgn0000212	brm	4	FBgn0004050	z	3	FBgn0032492	Prosalpha6T	2
FBgn0003448	sna	4	FBgn0011260	Sema-2a	3	FBgn0031872	iHog	2
FBgn0011640	lark	4	FBgn0024728	Slip1	3	FBgn0011766	E2f	2
FBgn0014396	tim	4	FBgn0011300	babo	3	FBgn0250785	vari	2
FBgn0036224	Rpt4R	4	FBgn0000560	eg	3	FBgn0250788	beta-Spec	2
FBgn0035849	ERR	4	FBgn0003415	skd	3	FBgn0001202	hk	2
FBgn0000472	dm	4	FBgn0003429	slo	3	FBgn0031985	CG8683	2
FBgn0086364	rdx	4	FBgn0003334	Scm	3	FBgn0016794	dos	2
FBgn0027356	Amph	4	FBgn0003430	slp1	3	FBgn0004870	bab1	2
FBgn0000179	bi	4	FBgn0003129	Poxm	3	FBgn0016797	fz2	2
FBgn0085448	Hmx	4	FBgn0032202	CG18619	3	FBgn0004882	orb	2
FBgn0026170	smt3	4	FBgn0002781	mod(mdg4)	3	FBgn0004606	zfh1	2
FBgn0250848	26-29-p	4	FBgn0053980	Vsx2	3	FBgn0023518	trr	2
FBgn0022238	lolal	4	FBgn0003896	tup	3	FBgn0001269	inv	2
FBgn0000163	baz	4	FBgn0037981	Spt3	3	FBgn0032651	Oli	2
FBgn0002940	ninaE	4	FBgn0000382	csw	3	FBgn0016081	fry	2
FBgn0028642	esn	4	FBgn0001624	dlg1	3	FBgn0008649	dei	2
FBgn0025458	BubR1	4	FBgn0004106	cdc2	3	FBgn0019968	Khc-73	2
FBgn0259217	Csk	4	FBgn0030695	PGRP-LE	3	FBgn0015618	Cdk8	2
FBgn0000022	ac	4	FBgn0050011	gem	3	FBgn0038063	Octbeta2R	2
FBgn0002985	odd	4	FBgn0039923	MED26	3	FBgn0013591	Mi-2	2
FBgn0011771	Hem	3	FBgn0003862	trx	3	FBgn0040388	boi	2
FBgn0029711	Usf	3	FBgn0000251	cad	3	FBgn0023531	CG32809	2
FBgn0015542	sima	3	FBgn0039936	CG11148	3	FBgn0259174	Nedd4	2
FBgn0003366	sev	3	FBgn0016917	Stat92E	3	FBgn0003380	Sh	2
FBgn0015550	tap	3	FBgn0002914	Myb	3	FBgn0016977	spen	2
FBgn0003475	spir	3	FBgn0020510	Abi	3	FBgn0051619	CG31619	2
FBgn0011763	Dp	3	FBgn0017578	Max	3	FBgn0003943	Ubi-p63E	2

Table D.2. Degree distribution of the proteins in the reconstructed Hedgehog network-continued

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0003687	Tbp	2	FBgn0039286	dan	2	FBgn0086655	jing	1
FBgn0021760	chb	2	FBgn0042650	disco-r	2	FBgn0086680	vvl	1
FBgn0003145	prd	2	FBgn0005558	ey	2	FBgn0001148	gsb	1
FBgn0024432	Dlc90F	2	FBgn0000721	for	2	FBgn0004387	Klp98A	1
FBgn0011276	HLH3B	2	FBgn0010300	brat	2	FBgn0259176	bun	1
FBgn0003977	vir	2	FBgn0004915	TfIIB	2	FBgn0032475	Sfmbt	1
FBgn0036671	CG9951	2	FBgn0022740	HLH54F	2	FBgn0085386	CG34357	1
FBgn0015589	Apc	2	FBgn0000157	Dll	2	FBgn0023522	CG11596	1
FBgn0003425	sli	2	FBgn0033260	Cul-4	2	FBgn0041205	key	1
FBgn0024321	NK7.1	2	FBgn0002932	neur	2	FBgn0003391	shg	1
FBgn0026319	Traf4	2	FBgn0000606	eve	2	FBgn0034400	CG15099	1
FBgn0039907	lgs	2	FBgn0036497	ran-like	2	FBgn0037672	sage	1
FBgn0028386	cic	2	FBgn0020381	Dredd	2	FBgn0011836	Taf2	1
FBgn0003023	otu	2	FBgn0034802	CG3800	2	FBgn0061173	fd3F	1
FBgn0039209	CG13624	2	FBgn0020386	Pk61C	2	FBgn0037466	CG1965	1
FBgn0003118	pnt	2	FBgn0028789	Doc1	2	FBgn0003941	RpL40	1
FBgn0029878	Pat1	2	FBgn0035424	CG11505	2	FBgn0038418	pad	1
FBgn0003720	tll	2	FBgn0260934	par-1	2	FBgn0259481	Mob2	1
FBgn0000411	D	2	FBgn0023214	edl	2	FBgn0003169	put	1
FBgn0000414	Dab	2	FBgn0000028	acj6	2	FBgn0037377	CG1218	1
FBgn0024330	MED6	2	FBgn0086897	sqd	1	FBgn0011577	dally	1
FBgn0015371	chn	2	FBgn0029708	CG3556	1	FBgn0036799	CG13380	1
FBgn0003511	Sry-beta	2	FBgn0004878	cas	1	FBgn0037475	Fer1	1
FBgn0039016	Dcr-1	2	FBgn0250786	Chd1	1	FBgn0034534	maf-S	1
FBgn0000242	Bx	2	FBgn0034728	rad50	1	FBgn0000448	Hr46	1
FBgn0036349	SNCF	2	FBgn0027066	Eb1	1	FBgn0086711	mol	1
FBgn0025680	cry	2	FBgn0011606	Klp3A	1	FBgn0044323	Cka	1
FBgn0000233	btd	2	FBgn0031851	CG11188	1	FBgn0011259	Sema-1a	1
FBgn0259750	ab	2	FBgn0004607	zfh2	1	FBgn0004512	Mdr49	1
FBgn0001085	fz	2	FBgn0087002	Rfabg	1	FBgn0004053	zen	1
FBgn0039038	CG6688	2	FBgn0053936	CG33936	1	FBgn0017581	Lk6	1
FBgn0033073	bin3	2	FBgn0004959	phm	1	FBgn0033015	d4	1
FBgn0036558	mib1	2	FBgn0032467	CG9934	1	FBgn0003545	sub	1
FBgn0003600	Su(var)3-9	2	FBgn0051792	CG31792	1	FBgn0037937	Fer3	1
FBgn0003607	Su(var)205	2	FBgn0015600	toc	1	FBgn0037751	topi	1
FBgn0037093	CG7597	2	FBgn0004364	18w	1	FBgn0000459	disco	1
FBgn0037094	CG7611	2	FBgn0040232	cmet	1	FBgn0024245	dnt	1
FBgn0003986	vnd	2	FBgn0001325	Kr	1	FBgn0003964	usp	1
FBgn0086902	kis	2	FBgn0024909	Taf7	1	FBgn0001297	kay	1
FBgn0002922	nau	2	FBgn0038197	foxo	1	FBgn0086442	mib2	1
FBgn0027548	nito	2	FBgn0008635	betaCop	1	FBgn0025632	CG4313	1
FBgn0002121	l(2)gl	2	FBgn0024291	Sir2	1	FBgn0040918	Lag1	1
FBgn0039066	EloA	2	FBgn0004666	sim	1	FBgn0024184	unc-4	1
FBgn0040466	Dip2	2	FBgn0053531	Ddr	1	FBgn0011591	fng	1
FBgn0013759	Caki	2	FBgn0052532	CG32532	1	FBgn0015331	abs	1

Table D.2. Degree distribution of the proteins in the reconstructed Hedgehog network-continued

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0024846	p38b	1	FBgn0000370	crc	1	FBgn0250843	Pros35	1
FBgn0025741	plexA	1	FBgn0003749	trh	1	FBgn0034821	CG9876	1
FBgn0002791	mr	1	FBgn0036134	Mnf	1	FBgn0000183	BicD	1
FBgn0003900	twi	1	FBgn0052105	CG32105	1	FBgn0004914	Hnf4	1
FBgn0001994	crp	1	FBgn0003612	Su(var)2-10	1	FBgn0035956	Doc2	1
FBgn0003031	pAbp	1	FBgn0026611	AGO1	1	FBgn0035021	CG4622	1
FBgn0003520	stau	1	FBgn0020309	crol	1	FBgn0035954	Doc3	1
FBgn0026323	Tak1	1	FBgn0003861	trp	1	FBgn0052280	CG32280	1
FBgn0015381	dsf	1	FBgn0014143	croc	1	FBgn0002945	nkd	1
FBgn0003326	sca	1	FBgn0037811	CG12592	1	FBgn0002941	slou	1
FBgn0003328	scb	1	FBgn0039938	Sox102F	1	FBgn0010452	trn	1
FBgn0011674	insc	1	FBgn0002723	Met	1	FBgn0000061	al	1
FBgn0000206	boss	1	FBgn0002521	pho	1	FBgn0005694	Aef1	1
FBgn0011725	twin	1	FBgn0029114	Tollo	1	FBgn0028999	nerfin-1	1
FBgn0024836	stan	1	FBgn0000289	cg	1	FBgn0023388	Dap160	1
FBgn0000346	comt	1	FBgn0053548	msta	1	FBgn0085410	CG34381	1
FBgn0030600	hiw	1	FBgn0005511	mid	1	FBgn0000140	asp	1
FBgn0015396	jumu	1	FBgn0024510	dlt	1	FBgn0034160	CG5550	1
FBgn0036697	rogdi	1	FBgn0030343	ATP7	1	FBgn0039767	CG2218	1
FBgn0003339	Scr	1	FBgn0027574	CG5815	1	FBgn0036254	CG5645	1
FBgn0003502	Btk29A	1	FBgn0000658	fj	1	FBgn0004197	Ser	1
FBgn0030899	Her	1	FBgn0000659	fkh	1	FBgn0002873	mud	1
FBgn0003300	run	1	FBgn0020224	Cbl	1	FBgn0027609	morgue	1
FBgn0003254	rib	1	FBgn0002924	ncd	1	FBgn0026597	Axn	1
FBgn0015567	alpha-Adaptin	1	FBgn0026404	Nc	1	FBgn0026598	Apc2	1
FBgn0001978	stc	1	FBgn0010349	Dhc64C	1	FBgn0004394	pdm2	1
FBgn0003053	peb	1	FBgn0000097	aop	1	FBgn0035518	CG15011	1
FBgn0000210	br	1	FBgn0011236	ken	1	FBgn0052343	CG32343	1
FBgn0003512	Sry-delta	1	FBgn0039170	CG13609	1			
FBgn0021875	Zfrp8	1	FBgn0001077	ftz	1			
FBgn0039601	CG1523	1	FBgn0027343	fz3	1			
FBgn0259234	Camta	1	FBgn0030018	slpr	1			
FBgn0011655	Med	1	FBgn0035989	CG3967	1			
FBgn0011747	Ank	1	FBgn0053169	CG33169	1			
FBgn0002780	mod	1	FBgn0000497	ds	1			
FBgn0010391	Gtp-bp	1	FBgn0025525	bab2	1			
FBgn0003651	svp	1	FBgn0038341	CG14869	1			
FBgn0043900	pygo	1	FBgn0020255	ran	1			
FBgn0003317	sax	1	FBgn0085445	Ank2	1			
FBgn0003042	Pc	1	FBgn0010441	pll	1			
FBgn0034476	Toll-7	1	FBgn0026175	skpC	1			
FBgn0039946	ATbp	1	FBgn0038928	BG4	1			
FBgn0025681	CG3558	1	FBgn0010575	sbb	1			
FBgn0004102	oc	1	FBgn0034926	CG5591	1			
FBgn0028550	A3-3	1	FBgn0027535	botv	1			

APPENDIX E: PROTEINS IN THE SHORTEST LINEAR PATHS

Table E.1. The proteins included in the shortest Wnt linear paths

	Proteins					
linear path 1	wg	fz	dsh	Ubx	arm	pan
linear path 2	wg	fz	dsh	Ubx	nmo	pan
linear path 3	wg	fz	dsh	Axn	arm	pan
linear path 4	wg	fz2	tj	HLHm7	gro	pan
linear path 5	wg	fz2	ptc	EcR	CycD	pan
linear path 6	wg	fz2	ptc	EcR	Cul-2	pan
linear path 7	wg	fz2	ptc	MEP-1	Cul-2	pan

Table E.2. The proteins included in the shortest Hedgehog linear path

	Proteins		
linear path 1	hh	fu	ci

APPENDIX F: PARTICIPATION PERCENTAGES OF THE PROTEINS IN THE LINEAR PATHS

Table F.1. The percentages of each protein contributing to the linear paths in Wnt/β-catenin network

Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)
pan	100,00	brk	5,30	Dl	1,95
arm	100,00	sna	5,18	sec5	1,87
wg	100,00	phyl	5,09	skpA	1,75
fz2	67,94	cnn	5,05	esg	1,75
ptc	54,42	ena	4,94	Mnt	1,73
dsh	36,92	CycD	4,73	HLHmgamma	1,73
nej	34,77	brm	4,73	lig3	1,68
fz	32,10	Doa	4,70	RpS27A	1,65
Ubx	30,10	gnu	4,65	tou	1,63
ttk	21,20	zf30C	4,60	odd	1,60
spn-A	19,82	Cul-2	4,39	14-3-3zeta	1,56
pont	17,79	tamo	4,34	cact	1,54
Apc	17,76	su(Hw)	4,28	Mad	1,49
tj	17,30	sgg	4,22	hth	1,42
Mer	16,77	dx	4,21	dl	1,40
sina	15,07	kn	4,21	Vsx2	1,38
N	14,38	CkIIbeta	4,20	opa	1,37
lgs	14,07	ebi	3,91	ERR	1,35
Axn	12,35	rin	3,79	Mi-2	1,35
Mical	11,13	Unc-89	3,75	MED26	1,30
Tsp	10,94	exd	3,75	so	1,30
Snr1	10,68	osa	3,70	Lim1	1,28
arr	10,48	Hsc70-4	3,63	CG33967	1,27
ci	9,49	pUf68	3,44	Ank	1,07
MEP-1	9,49	Tab2	2,98	lola	1,07
Act5C	9,35	noc	2,98	Dll	1,05
Sox21b	9,29	Csk	2,96	Zn72D	1,05
p53	8,39	danr	2,88	CG31999	1,03
E2f2	8,32	E(spl)	2,73	Chc	1,01
dimm	8,16	apt	2,64	Atpalpha	1,01
CtBP	7,78	babo	2,59	CG32486	0,97
Akt1	7,77	E5	2,56	CG15800	0,95
sol	7,66	sd	2,51	bi	0,90
HLHm7	7,47	HLH4C	2,42	Smox	0,87
h	7,30	chinmo	2,37	Rap2l	0,86
bcd	7,00	gt	2,31	aret	0,86
bip2	6,96	Hrs	2,31	hiw	0,84
gro	6,89	Bap	2,09	H2.0	0,83
MED17	6,83	esn	2,08	RhoGAP92B	0,82
Moe	6,62	nmo	2,07	da	0,82
PHDP	6,58	CkIIalpha	2,04	CG4328	0,81
sinah	6,05	HLHm3	2,03	en	0,79
toy	5,66	HLHmdelta	2,02	dsx	0,78
EcR	5,50	HLHmbeta	1,98	Taf1	0,76
e(y)3	5,36	HLHm5	1,96	CadN	0,75

Table F.1. The percentages of each protein contributing to the linear paths in Wnt/β-catenin network-continued

Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)
lbl	0,73	LpR1	0,33	slp1	0,15
polo	0,67	rdx	0,33	ftz-f1	0,15
CG3731	0,67	ac	0,32	CG7056	0,15
ago	0,65	C15	0,32	Anxb11	0,14
dpn	0,61	pzg	0,31	ara	0,14
Stat92E	0,59	beta-Spec	0,29	CG32392	0,14
ab	0,59	Atf-2	0,28	Ddr	0,14
Rala	0,58	bsk	0,28	lark	0,14
ey	0,58	Roc1a	0,27	Hsp83	0,13
tup	0,55	Trf	0,27	wek	0,13
mbt	0,55	pros	0,27	mib1	0,12
th	0,54	lok	0,27	CG11148	0,12
CHIP	0,54	drk	0,27	zen	0,12
knrl	0,54	cnc	0,25	nau	0,12
dei	0,52	CG32532	0,24	Doc1	0,12
prd	0,51	HLH54F	0,23	alpha-Cat	0,12
mod(mdg4)	0,51	Nf-YC	0,22	kst	0,12
Pros45	0,48	Lim3	0,22	Rfx	0,12
lolal	0,46	Cp190	0,22	CG18619	0,12
MED6	0,46	fu	0,22	CG34340	0,12
Fmr1	0,45	lin19	0,21	Pif1B	0,11
pAbp	0,45	eg	0,21	Ank2	0,11
sc	0,45	east	0,21	dlg1	0,11
elB	0,44	Rlip	0,21	cm	0,10
Dfd	0,43	cad	0,20	Sir2	0,10
TflIB	0,42	Su(H)	0,20	Usf	0,10
nuf	0,42	ato	0,19	bowl	0,10
cos	0,41	BicC	0,19	eIF-4a	0,10
Hey	0,40	eyg	0,18	Hmx	0,10
Gsc	0,38	X11L	0,18	emc	0,09
Myb	0,38	BM-40-SPARC	0,18	eve	0,08
cup	0,38	Mob2	0,18	smt3	0,08
RhoGEF2	0,38	Amph	0,17	Su(fu)	0,08
Tektin-A	0,37	Nedd4	0,17	Bin1	0,08
amos	0,36	Trl	0,17	H	0,08
dpp	0,36	CG34422	0,17	inv	0,08
kni	0,36	Max	0,17	E(z)	0,07
ase	0,35	par-6	0,17	Nf-YA	0,07
chn	0,35	for	0,17	fj	0,07
peb	0,35	BubR1	0,17	aPKC	0,07
e(r)	0,35	Nc	0,16	orb	0,07
bin3	0,34	Dip2	0,15	Hem	0,06
CG2678	0,34	tim	0,15	MED20	0,06
raps	0,34	fd59A	0,15	tll	0,05
fry	0,34	z	0,15	CG13624	0,05

Table F.1. The percentages of each protein contributing to the linear paths in Wnt/β-catenin network-continued

Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)
NK7.1	0,05	Ets97D	0,02	HLH3B	0,002
tap	0,05	G-oalpha47A	0,02	Rpt4	0,002
robo	0,05	Pros26.4	0,02	csw	0,002
mud	0,05	Rpt4R	0,02	vvl	0,002
sli	0,05	bab1	0,02	CLIP-190	0,002
CG31619	0,05	Dcr-1	0,02	Cdk8	0,002
oc	0,05	Vap-33-1	0,02	plexA	0,002
cry	0,05	Rfabg	0,014	gbb	0,002
bsh	0,05	hk	0,014	dos	0,002
dco	0,05	EloA	0,014	acj6	0,002
zfh1	0,04	Sos	0,014	loqs	0,002
disco-r	0,04	Su(var)205	0,014	CG1894	0,002
Jra	0,04	Poxm	0,014	jar	0,002
dm	0,04	CG7611	0,014		
Rac1	0,04	fd64A	0,014		
Nrg	0,04	cdc2	0,014		
ed	0,04	rho-4	0,012		
slmb	0,04	AGO1	0,012		
Slip1	0,04	ATbp	0,010		
Arf51F	0,04	chb	0,010		
Pcl	0,04	par-1	0,010		
CG2478	0,04	Traf6	0,010		
ran-like	0,03	slo	0,010		
Dp	0,03	esc	0,010		
Rbf	0,03	per	0,010		
mip130	0,03	Sema-2a	0,007		
Rbf2	0,03	D	0,007		
RpL40	0,03	smo	0,007		
Drep-3	0,03	CG5641	0,005		
CG5645	0,03	Taf12	0,005		
sima	0,03	Octbeta2R	0,005		
neur	0,03	Su(var)3-9	0,005		
CG1523	0,03	l(2)NC136	0,005		
ninaE	0,03	ph-p	0,005		
Ubi-p63E	0,03	baz	0,005		
Wnt5	0,03	l(2)gl	0,005		
slpr	0,03	abs	0,005		
fd3F	0,02	sofe	0,005		
Cdc42	0,02	vari	0,005		
kto	0,02	Rpd3	0,005		
numb	0,02	stc	0,005		
Pka-R2	0,02	Act87E	0,005		
spir	0,02	Pka-C1	0,005		
wee	0,02	sip2	0,005		
skd	0,02	fru	0,002		

Table F.2. The percentages of each protein contributing to the linear paths in Hedgehog network

Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)
hh	100.00	zf30C	7.26	E(spl)	2.87
ci	100.00	CHIP	6.55	E5	2.78
ptc	92.69	Cul-2	6.46	arm	2.73
ttk	29.84	elB	6.30	CG32486	2.56
lwr	29.72	CkIIalpha	6.10	brk	2.56
Mer	26.47	gro	6.04	sgg	2.53
spn-A	24.74	polo	5.88	Su(fu)	2.53
CtBP	18.96	slmb	5.81	ftz-f1	2.50
nej	18.14	bi	5.80	sd	2.49
fu	17.61	dsh	5.66	HLHmbeta	2.49
cact	16.70	exd	5.63	tj	2.34
cnn	16.26	Csk	5.32	CG11148	2.25
E2f2	16.18	noc	5.30	amos	2.18
Doa	15.48	Dl	5.16	tup	2.07
sina	15.26	HLHm7	4.74	CkIIbeta	2.05
bcd	15.15	CG4328	4.71	CG33967	1.92
dimm	15.01	RpS27A	4.63	fd59A	1.92
PHDP	15.00	Khc-73	4.48	fz2	1.84
danr	14.83	Taf1	4.46	so	1.81
p53	13.61	14-3-3zeta	4.43	CkIalpha	1.79
sinah	13.56	kni	4.39	esg	1.78
Mical	11.95	sol	4.33	nau	1.70
Akt1	11.58	aret	4.19	Doc1	1.70
N	11.57	CycD	4.02	HLHmgamma	1.69
phyl	11.33	opa	3.91	da	1.61
dl	11.10	Dfd	3.68	Stat92E	1.43
kn	10.89	bin3	3.68	ab	1.43
cos	10.83	rin	3.60	Myb	1.43
sna	10.56	prd	3.60	dco	1.38
Sox21b	10.08	Act5C	3.58	HLHm3	1.30
EcR	9.79	lin19	3.57	Roc1a	1.29
toy	9.01	MED26	3.54	wek	1.23
smo	8.94	dx	3.32	slp1	1.21
tamo	8.93	Hsc70-4	3.30	en	1.18
Pka-C1	8.82	Fmr1	3.30	C15	1.16
skpA	8.65	east	3.28	smt3	1.16
Moe	8.61	HLHm5	3.24	Pros45	1.16
ebi	8.55	tou	3.06	Lim3	1.15
hth	8.53	sip1	3.04	cup	1.14
pUf68	8.36	Kap-alpha3	3.01	slo	1.02
Ubx	8.20	HLHmdelta	2.99	cad	1.02
orb2	8.18	h	2.97	apt	1.02
Hrs	8.09	HLH4C	2.97	Dll	1.01
CG3731	7.90	Mnt	2.91	HLH3B	1.00
Tab2	7.76	lok	2.89	ago	0.97

Table F.2. The percentages of each protein contributing to the linear paths in Hedgehog network-continued

Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)	Protein	Percentage in linear paths (%)
tap	0.97	ERR	0.37	lolal	0.08
tim	0.96	z	0.37	par-1	0.08
SNCF	0.96	dlg1	0.35	zfh1	0.08
Su(H)	0.94	dpn	0.34	Pat1	0.07
babo	0.91	Hmx	0.30	spen	0.07
Mad	0.91	tll	0.30	CG7597	0.07
knrl	0.90	mod(mdg4)	0.29	Bx	0.07
Gsc	0.89	NK7.1	0.28	EloA	0.07
Dip2	0.86	ase	0.27	Max	0.05
bsk	0.86	cnc	0.27	H2.0	0.05
Vsx2	0.82	Ada2b	0.27	hk	0.04
fry	0.81	emc	0.26	par-6	0.04
CG15800	0.79	chn	0.23	aPKC	0.03
brm	0.76	Hsp83	0.23	Poxm	0.03
e(y)3	0.75	Dp	0.23	numb	0.03
lbl	0.75	Taf4	0.23	Octbeta2R	0.03
eg	0.74	Cul-4	0.22	Abi	0.03
CG34340	0.74	Hey	0.21	CG9951	0.02
mib1	0.74	gt	0.21	E2f	0.02
odd	0.73	Ubi-p63E	0.21	TfIIB	0.02
kto	0.72	ac	0.20	HLH54F	0.02
skd	0.72	nito	0.19	MED6	0.02
CG2678	0.72	Apc	0.19	csw	0.02
Khc	0.71	chb	0.19	Rpt4	0.02
CG7056	0.70	BicC	0.18	dos	0.02
dpp	0.70	cdc2	0.17	Rpt4R	0.02
otu	0.67	Hem	0.17	Rpt1	0.01
Lim1	0.64	Bin1	0.17	esc	0.01
per	0.63	gnu	0.17	pros	0.01
ran-like	0.63	CG8683	0.15	CG11505	0.01
beta-Spec	0.61	Slip1	0.14	brat	0.01
disco-r	0.57	for	0.14	e(y)1	0.01
RhoGAP92B	0.56	BubR1	0.14	Spt3	0.01
dsx	0.55	esn	0.14	rdx	0.01
26-29-p	0.55	Trl	0.13	Tbp	0.01
ara	0.54	ato	0.13	spir	0.01
wee	0.50	bsh	0.12	ph-p	0.01
drk	0.50	bowl	0.12	tgo	0.01
Klc	0.49	Ets97D	0.12	sima	0.01
eve	0.49	CG18619	0.12	ninaE	0.01
dei	0.47	Cdk8	0.12	Dab	0.003
nuf	0.46	Pros26.4	0.11	sev	0.003
Nedd4	0.44	Pif1B	0.11	baz	0.003
Amph	0.44	Nf-YA	0.10	CG32809	0.003
lark	0.43	orb	0.10	CG7611	0.002
Mi-2	0.41	E(z)	0.10	Prosalpha6T	0.002
D	0.40	Rpb4	0.10	l(2)gl	0.001
Nf-YC	0.40	CG13624	0.09	Rpd3	0.001
sc	0.40	vir	0.09	Su(z)12	0.001
lola	0.37	dm	0.08		

APPENDIX G: CROSSTALK ANALYSIS RESULTS

Table G.1. The common proteins between Wnt/β-catenin and Hedgehog signaling networks

Protein name	Protein name	Protein name	Protein name	Protein name	Protein name
ci	HLH4C	esc	numb	ninaE	CG18619
Mer	dimm	Ada2b	Su(fu)	esn	mod(mdg4)
ptc	cos	dpn	Fur2	BubR1	Vsx2
gro	CkIIbeta	CG2678	dsx	Csk	tup
CtBP	dsh	Taf1	hth	ac	Spt3
Moe	tj	sc	sd	odd	csw
ttk	nej	par-6	lin19	Hem	dlg1
HLHmbeta	h	nuf	elB	Usf	cdc2
sinah	brk	arm	knrl	sima	PGRP-LE
dl	wek	Rpt4	gnu	sev	gem
HLHm7	Mad	sgg	tgo	tap	MED26
toy	CkIIalpha	Sox21b	CG7056	spir	trx
spn-A	Fmr1	aPKC	drk	Dp	cad
N	fu	E5	hh	InR	CG11148
tamo	exd	ebi	CkIalpha	CG15800	Stat92E
cnn	Pros45	Rpd3	Nf-YC	e(y)3	Myb
skpA	CG4328	RhoGAP92B	Dfd	kni	Max
E2f2	so	Jra	emc	BEAF-32	pk
polo	Trl	opa	H2.0	kto	tou
HLHmgamma	Hsc70-4	cnc	Ets97D	CG34340	east
HLHm5	Dl	smo	Roc1a	ph-p	per
kn	ago	bsk	wee	Su(H)	robo
sol	Bin1	bsh	ird5	ara	cup
da	EcR	Lim1	Taf4	lbl	dpp
HLHm3	dx	Pka-C1	esg	gcm2	lok
bcd	pUf68	Nf-YA	rl	gt	ato
Ubx	Pros26.4	ftz-f1	brm	amos	e(y)1
Doa	lola	CycD	sna	dco	Su(z)12
cact	E(z)	Gsc	lark	en	Rpt1
E(spl)	14-3-3zeta	Pif1B	tim	CG33967	fd64A
Act5C	noc	danr	Rpt4R	z	bowl
phyl	Mnt	BicC	ERR	Sema-2a	pros
Hrs	fd59A	Lim3	dm	Slip1	Hsp83
Akt1	CG3731	CG32486	rdx	babo	sip2
HLHmdelta	Rpb4	Cul-2	Amph	eg	iHog
p53	CHIP	ase	bi	skd	E2f
Tab2	apt	zf30C	Hmx	slo	vari
PHDP	slmb	rin	smt3	Scm	beta-Spec
C15	RpS27A	Mical	lolal	slp1	hk
sina	Hey	aret	baz	Poxm	CG8683

Table G.1. The common proteins between Wnt/β-catenin and Hedgehog signaling networks-continued

Protein name	Protein name	Protein name	Protein name	Protein name	Protein name
dos	btd	CG11188	Lk6	Zfrp8	slpr
bab1	ab	zfh2	d4	CG1523	CG3967
fz2	fz	Rfabg	Fer3	Camta	CG33169
orb	CG6688	CG33936	topi	Med	bab2
zfh1	bin3	CG9934	disco	Ank	CG14869
trr	mib1	18w	dnt	mod	ran
inv	Su(var)3-9	Kr	usp	svp	Ank2
fry	Su(var)205	Taf7	kay	pygo	pll
dei	CG7597	foxo	mib2	sax	skpC
Cdk8	CG7611	Sir2	CG4313	Toll-7	BG4
Octbeta2R	vnd	sim	Lag1	ATbp	sbb
Mi-2	kis	Ddr	unc-4	CG3558	CG5591
CG32809	nau	CG32532	abs	oc	CG9876
Nedd4	l(2)gl	jing	p38b	A3-3	Hnf4
Sh	EloA	vvl	plexA	crc	Doc2
spen	Dip2	gsb	twi	trh	CG4622
CG31619	Caki	bun	crp	Mnf	Doc3
Ubi-p63E	dan	Sfmbt	pAbp	Su(var)2-10	CG32280
Tbp	disco-r	CG11596	stau	AGO1	nkd
chb	ey	key	Tak1	crol	slou
prd	for	shg	sca	trp	trn
HLH3B	brat	CG15099	scb	croc	al
CG9951	TfIIB	sage	insc	CG12592	Aef1
Apc	HLH54F	Taf2	boss	Sox102F	nerfin-1
sli	Dll	fd3F	twin	pho	Dap160
NK7.1	neur	CG1965	stan	Tollo	CG34381
Traf4	eve	RpL40	comt	cg	asp
lgs	ran-like	pad	hiw	mid	CG5550
cic	Dredd	Mob2	jumu	dlt	CG5645
CG13624	CG3800	put	rogdi	CG5815	Ser
pnt	Pk61C	CG1218	Scr	fj	mud
tll	Doc1	dally	Btk29A	fkh	morgue
D	par-1	CG13380	Her	Cbl	Axn
Dab	edl	Fer1	run	Nc	Apc2
MED6	acj6	maf-S	rib	Dhc64C	pdm2
chn	CG3556	Hr46	alpha-Adaptin	aop	CG15011
Sry-beta	cas	mol	stc	ken	CG32343
Dcr-1	Chd1	Cka	peb	CG13609	
Bx	Eb1	Sema-1a	br	ftz	
cry	Klp3A	zen	Sry-delta	fz3	

Table G.2. The signaling proteins that have non-zero network crosstalk values

FlyBase ID	Protein symbol	Degree	FlyBase ID	Protein symbol	Degree
FBgn0004859	ci	7	FBgn0032956	Cul-2	1
FBgn0086384	Mer	3	FBgn0028902	Tektin-A	1
FBgn0003892	ptc	3	FBgn0003371	sgg	1
FBgn0025637	skpA	3	FBgn0025743	mbt	1
FBgn0011661	Moe	2	FBgn0001981	esg	1
FBgn0019650	toy	2	FBgn0027338	Kap-alpha3	1
FBgn0010602	lwr	2	FBgn0086364	rdx	1
FBgn0035357	MEP-1	2	FBgn0035938	orb2	1
FBgn0250848	26-29-p	2	FBgn0026056	Rlip	1
FBgn0027548	nito	2	FBgn0011737	wee	1
FBgn0003870	ttk	1	FBgn0036224	Rpt4R	1
FBgn0003479	spn-A	1	FBgn0010342	Map60	1
FBgn0004647	N	1	FBgn0026170	smt3	1
FBgn0260632	dl	1	FBgn0004050	z	1
FBgn0003464	sol	1	FBgn0023531	CG32809	1
FBgn0003944	Ubx	1	FBgn0024432	Dlc90F	1
FBgn0000042	Act5C	1	FBgn0011276	HLH3B	1
FBgn0003410	sina	1	FBgn0036671	CG9951	1
FBgn0031450	Hrs	1	FBgn0010287	Trf	1
FBgn0040080	raps	1	FBgn0029878	Pat1	1
FBgn0011277	HLH4C	1	FBgn0036349	SNCF	1
FBgn0039044	p53	1	FBgn0259785	pzg	1
FBgn0025334	PHDP	1	FBgn0040466	Dip2	1
FBgn0000352	cos	1	FBgn0085451	CG34422	1
FBgn0001079	fu	1	FBgn0004512	Mdr49	1
FBgn0000578	ena	1	FBgn0035975	PGRP-LA	1
FBgn0010235	Klc	1	FBgn0037734	trbd	1
FBgn0036274	CG4328	1	FBgn0000810	fs(1)K10	1
FBgn0015805	Rpd3	1	FBgn0250843	Pros35	1
FBgn0024191	sip1	1	FBgn0026080	Tip60	1
FBgn0028577	pUf68	1			

APPENDIX H: ALGORITHMS AND SCRIPTS

H.1. NetSearch Script

-if: interaction file
-mf: membrane protein (ligand) file
-tf: transcription factor file
-cf: cluster (proteins) file
-o: output file
-lm: minimum path length
-l: maximum path length

Script: netsearch -cf proteins.txt -if interactions.txt -mf ligand.txt -tf transcription.txt -lm 2 -l 12 -o output.txt

H.2. Script for the Calculation of Participation Percentages

```
Public Function numORF(orfname As String)
'i shows column number
Dim rownum
Dim colnum
sumnonzero = 0
For rownum = 1 To 41486
   For colnum = 1 To 12
      If Cells(rownum, colnum) = orfname Then
       sumnonzero = sumnonzero + 1
      End If
   Next colnum
 Next rownum
numORF = sumnonzero
End Function
```

H.3. MCODE Algorithm and Running Parameters

H.3.1. Algorithm

Stage 1: Vertex weighting

```
procedure MCODE-VERTEX-WEIGHTING
        input: graph: G = (V,E)
        for all v in G do
                N = Find neighbors of v to depth 1
                K = Get highest k-core graph from N
                k = Get highest k-core number from N
                d = Get density of K
                Set weight of v = k x d
        end for
end procedure
```

Stage 2: Molecular Complex Prediction

```
procedure MCODE-FIND-COMPLEX
        input: graph: G = (V,E); vertex weights: W;
                vertex weight percentage: d; seed vertex: s
        if s already seen then return
        for all v neighbors of s do
                if weight of v > (weight of s)(1-d) then add v to complex C
                call: MCODE-FIND-COMPLEX (G,W,d,v)
        end for
end procedure
procedure MCODE-FIND-COMPLEX
        input: graph: G = (V,E); vertex weights: W;
                vertex weight percentage: d
        for all v in G do
                if not already seen v then call: MCODE-FIND-COMPLEX (G,W,d,v)
        end for
end procedure
```

Stage 3: Post-Processing (optional)
procedure MCODE-POST-PROCESS
input: graph: G=(V,E); vertex weights: W; haircut flag: *h*;
set of predicted complex graphs: C
for all *c* in C do
if *c* not 2-core then filter
if *h* is TRUE then 2-core complex
end for
end procedure

H.3.2. Running Parameters

vertex weight percentage: 0.2
haircut: TRUE

H.4. Running Parameters of the BİNGO Algorithm

Ontology: Molecular function
Curator: GO
Selected annotation file: gene_association.fb.gz (January, 2010)
Selected statistical test: Hypergeometric test
Selected significance level, *p*-value: 0.05
Testing option: Test cluster (module) versus whole annotation

H.5. Schematic Representation of the Network Crosstalk

Network crosstalk value of the node a = (the degree of this node in the combined pathway) - (the maximum degree of this node in any one individual pathway)
Network crosstalk value of the node a = 7 - 5 = 2

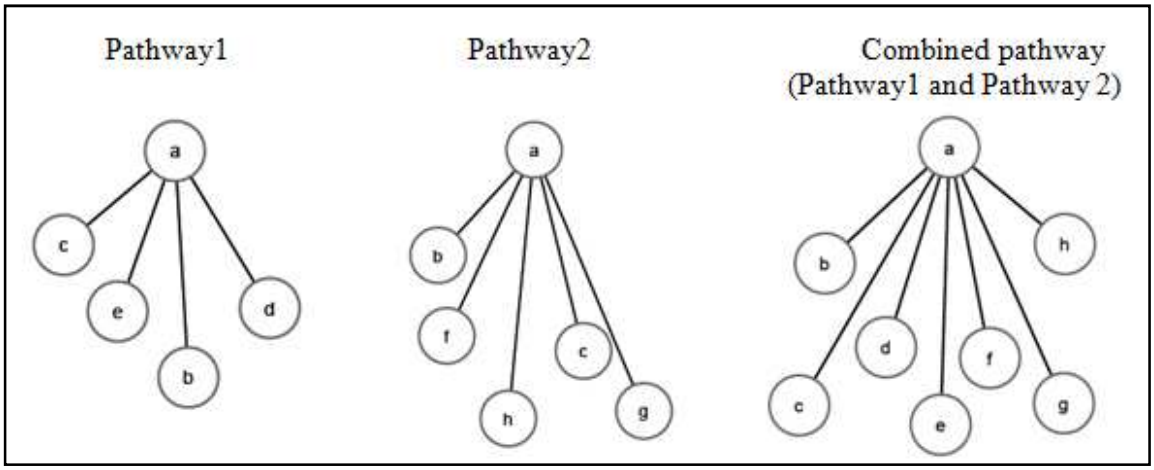


Figure H.1. Schematic representation of the network crosstalk

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