Article

Construction and analysis of the protein-protein interaction network of visual system in Drosophila

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Abstract
Insects are one of the most widely distributed animals on earth, and their visual systems have strong adaptability, deeply affecting their survival, reproduction, diet, and environmental adaptation. With the sequencing of the entire genome of Drosophila and the development of modern biotechnology, research on visual proteins has made significant progress. Currently, a large amount of visual protein data has been obtained through conventional experimental methods and high-throughput analysis technology, but the functions of most visual proteins are still unannotated. In addition, the current research focus mostly on individual proteins or single interactions, and there has been no comprehensive analysis of visual proteins as a whole. Therefore, in this article we used network biology methods to construct the protein-protein interaction network of visual system in Drosophila and further determine the crucial proteins in the network. We have mainly obtained seed proteins by searching a large number of literature related to visual proteins in Drosophila, and used the STRING database to obtain information on protein-protein interactions to construct the protein-protein interaction network of visual system. The clusterProfiler software package was used for functional enrichment analysis. The protein-protein interaction network constructed using Cytoscape software included 248 proteins and 2948 interactions, and the crucial proteins in the network are Akt1, arm, Src42A, Pten, Rho1, norpA, and Egfr, etc. They are crucial visual proteins in Drosophila. These proteins play an important role in the network structure. The results showed that visual proteins play an important role in biological rhythms, morphogenesis, and basic metabolism of the insect.

Keywords Drosophila; visual system; protein-protein interaction network; network construction; network analysis; crucial proteins.

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1 Introduction

Vision is a complex biological process. It can not only recognize the shape and color of the host plant, but also perceive information such as light intensity and direction in the surrounding environment, and guide animals to find food, avoid natural enemies, and perform normal life activities such as mating. The visual system is very

sensitive to various colors and brightness, and they can capture and distinguish light changes and stimuli in a short time (Homberg, 2020). Visual proteins are performers of visual functions. So far, a large number of studies on visual proteins and genes have been carried out, which has laid a foundation for understanding animal visual perception and further revealing its visual mechanism (Fischbach and Dittrich, 1989; Burg et al., 1993; Bonini et al., 1993; Halder et al., 1995; Niemeyer et al., 1996; Zuker, 1996; Clandinin and Zipursky, 2002; Borycz et al., 2002; Gegenfurtner and Kiper, 2003; Dominguez et al., 2004; Pappu and Mardon, 2004; Kracklauer et al., 2007; Osorio and Vorobyev, 2008; Borst, 2009; Strausfeld, 2009; Oros et al., 2010; Shieh, 2011; Fan et al., 2014; Yamamoto and Seto, 2014; Schopf and Huber, 2017; de Andres-Bragado and Sprecher, 2019; Xu and Wang, 2019; Schnaitmann et al., 2020; Wienecke and Clandinin, 2020; Sang et al., 2021; Smylla et al., 2021; Konstantinides et al., 2022).

Drosophila is one of the commonly used model organisms, and its visual system is also an important model in research. It has a good research foundation in the functions and regulatory mechanisms of visual proteins. Its complex visual receptor mechanism not only has a high degree of structural and functional precision, but also is closely connected with multiple neurotransmitters and signaling pathways, which allows researchers to learn from the characteristics of its visual system and explore various theoretical models and practical applications. In-depth research on the visual system of Drosophila will help us understand the basic biological mechanisms of light perception and behavioral selection, and provide new ideas and methods for the diagnosis and treatment of related human diseases.

1.1 Visual system of Drosophila

1.1.1 Visual receptors

The visual system of Drosophila is a type of receptor in the form of compound eyes, consisting of a pair of giant compound eyes and three ocelli. The compound eye is composed of a series of individual ommatidia, each containing six keratinocytes, one pigment cell, and one lens cell. These cells are able to independently receive and process light signals and transmit them to the nervous system for decoding and analysis. The resolution of the compound eyes of Drosophila is very high, with an average single eye containing about 76,000 receptor cells, so they can quickly and accurately perceive objects and movements in the natural environment.

The visual system of Drosophila is one of the best-studied objects in insects. Its retina consists of about 800 cells, each containing a visual receptor cell and six surrounding pigment cells. Each visual receptor cell contains a retinal receptor, called Rhodopsin, along with other signaling molecules that participate in a signal transduction pathway in the photoreceptors that converts external light signals into nerve electrical signals (Kristaponyte et al., 2012).

In Drosophila, neurons in the retina transmit images to the central nervous system for processing and analysis based on information picked up by different types of photoreceptor cells. In addition, the researchers found that the cone cells (cone cells) in the compound eyes of Drosophila are very sensitive to color recognition and perception. By comparing the response patterns of different types of cone cells, it is possible to infer how Drosophila perceives color (Briscoe and Chittka, 2001; Stavenga, 2002).

Drosophila's single eye is located in the top center of the head and is mainly used to perceive the intensity and direction of light. Monocular eyes have lower resolution and sensitivity than compound eyes, but they can provide additional spatial orientation information that helps flies stabilize during flight (Borst and Haag, 2002).

The visual receptors of Drosophila larvae are mainly composed of two parts: eyes and photoreceptors. The eye of a Drosophila larva consists of a single convex lens located at the front of the head. There are 12 photoreceptor cells in each eye, arranged in a hexagon to form a retina. These photoreceptors can detect

different wavelengths of light, known as colored light (Kirkhart and Scott, 2015). The photoreceptors of Drosophila larvae are located on the surface of the body and are distributed throughout the body, especially in the head and tail. These photoreceptors can detect low light in the environment and respond to it. When light hits them, these photoreceptors generate electrical signals that relay information to the nervous system.

1.1.2 Alternative expression of visual receptor genes

The selective expression of visual receptor genes in Drosophila is regulated by multiple signaling pathways and may involve different transcription factors and signaling molecules. In Drosophila, the development and function of visual receptor cells depend on eye-specific transcription factors and other interacting proteins. These transcription factors, proteins, and signaling molecules can form complex regulatory networks, in which the activity of different motifs or motifs at time points can produce different visual perception outcomes.

The selective expression of Drosophila's visual receptor genes is a complex process involving the regulation of multiple signaling pathways. These regulatory factors can affect the promoter activity of genes encoding visual receptors, and may function at different time points and tissues, thereby affecting the perception and behavioral responses of Drosophila to ambient light.

For example, the INAD protein, a protein with multiple PDZ domains, acts as a bridge to connect different signaling pathways in Drosophila's visual receptor cells, thereby promoting signal transduction in photoreceptors. The organization of the INAD signaling complex is critical to ensure the sensitivity and speed of visual signaling (Tsunoda and Zuker, 1999).

In addition, Arrestin1 plays an important role in Drosophila's phototransduction. Studies have shown that Arrestin1 mediates light-dependent Rhodopsin endocytosis and cell survival, and can regulate its function through various signaling pathways (Satoh and Ready, 2005; Kristaponyte et al., 2012).

In addition to these signaling molecules, there are other factors that can affect the selective expression of Drosophila's visual receptor genes. For example, certain environmental factors, genetic variation, and natural selection may all affect the expression of visual receptors in Drosophila. Therefore, in-depth study of the mechanism of selective expression of Drosophila's visual receptor genes is of great significance for understanding how the insect's visual system adapts to different environments and tasks.

1.2 Brief overview on visual proteins in Drosophila

Drosophila is one of the commonly used model organisms, and its visual system is also an important model in research. In Drosophila, a variety of visual proteins have been discovered, and the functions and regulatory mechanisms of these proteins have been studied in depth.

A visual receptor gene family has been identified in Drosophila, including about 30 genes encoding visual receptor proteins. These visual receptor proteins are expressed in the photoreceptor neurons of Drosophila and can recognize different wavelengths of light, thereby guiding the behavioral choices of Drosophila.

In addition to visual receptor proteins, some auxiliary proteins also play an important role in the visual system of Drosophila. For example, INAD proteins facilitate the transmission of visual signals by assembling optical signaling complexes (Tsunoda and Zuker, 1999). In addition, Rhodopsin Kinase (RK) and Arrestin2 can inhibit the activity of visual receptor proteins through a negative feedback mechanism, thereby regulating the sensitivity to different light (Palczewski et al., 1992; Satoh et al., 2010; Kristaponyte et al., 2012).

In recent years, some studies have also focused on more basic biological processes in the visual system of Drosophila. For example, several studies have shown that visual perception in Drosophila is also influenced by time and space (Eichner et al., 2011; Li et al., 2013).

1.2.1 Opsins

Opsins are one of the most important proteins in the visual system of Drosophila (O'Tousa et al., 1985). They are membrane proteins encoded by a series of genes, which can absorb different wavelengths of light and

convert them into neural signals, thereby realizing the perception and behavioral responses of insects to the external environment. Opsins are mainly found in the compound eyes of Drosophila. Different types of opsins absorb different wavelengths of light, ranging from ultraviolet to infrared. In addition, opsins work with Chromophore-binding proteins to convert light energy into neural signals (Wernet et al., 2015).

As early as the 1970s, scientists began using Drosophila as a research model to explore the insect's visual system (Fritz et al., 1998). In the early 1980s, Fritz et al. first isolated opsin from the eye of Drosophila and determined its amino acid sequence. Since then, people have gradually discovered various opsins in the visual system of Drosophila, including long-wavelength opsin (LW-opsin), medium-wavelength opsin (MW-opsin) and short-wavelength opsin (SW-opsin) (Stocker, 1994).

Opsins play a very important role in the survival and reproduction of Drosophila. They can perceive light signals in the external environment and transmit them to the central nervous system of Drosophila through the nervous system, thereby triggering behavioral responses. For example, Drosophila relies on its visual system to judge its surroundings in finding food, avoiding danger, and reproducing (Silies et al., 2013).

In recent years, with the continuous development of genetics, optics and imaging technology, the research on the visual system of Drosophila is also deepening. For example, recent studies have shown that the presynaptic signal transduction mechanism in Drosophila's visual cells is very complex, involving multiple signaling pathways and protein interactions (Silies et al., 2013). In addition, some researchers have successfully achieved single-cell recording of visual neurons in Drosophila by using genetic technology and laser interference technology.

1.2.2 Chromophore-binding proteins

Chromophore-binding proteins are an important protein type in the visual system of Drosophila, which mainly exists in the compound eyes of Drosophila, and together with opsin constitute the visual cells. They bind to opsins to form a photon-absorbing complex that converts light energy into electrical signals. Each chrome-binding protein corresponds to a type of opsin that absorbs specific wavelengths of light. For example, Rh5 combined with MW-opsin can absorb green light, while Rh6 combined with LW-opsin is sensitive to red light.

Pigment-binding protein was first isolated in Drosophila in 1993. Subsequently, more and more pigment-binding proteins have been identified, and four different types of pigment-binding proteins have been found in Drosophila: Rhodopsin5 (Rh5), Rhodopsin6 (Rh6), Rhodopsin7 (Rh7) and Cryptochrome (Cry) (Kristaponyte et al., 2012; Montell, 2012). Studies have shown that the interaction of chromopin and opsin is a very complex process involving multiple signaling pathways and protein interactions. Some researchers have discovered the different roles and regulatory mechanisms of these two pigment-binding proteins in the visual system of Drosophila through mutation experiments on the Rh5 and Rh6 genes. A specific example is the binding of Rhodopsin5 (Rh5) and Rhodopsin6 (Rh6) to opsins. In the compound eye of Drosophila, Rh5 and Rh6 each form a complex with a common opsin, the long-wave absorbing opsin Rhodopsin1 (Rh1). Rh5 and Rh6 have different sensitivities to light of different wavelengths, among which Rh5 mainly absorbs blue and ultraviolet rays, while Rh6 mainly absorbs green and yellow. When light shines on these pigment-binding proteins, they undergo a conformational change, activate the corresponding opsin Rh1, and transmit signals to the brain through the optic nerve, producing images.

In addition, there is another pigment-binding protein, Cryptochrome (Cry), in the visual system of Drosophila, which can absorb blue light and participate in the regulation of the circadian clock. When Cry absorbs blue light, it forms a complex and controls the circadian rhythm of Drosophila by regulating the expression of other genes (Ceriani et al., 1999).

Pigment-binding protein plays a very important role in the visual system of Drosophila. They are not only

the key components of visual cells, but also can convert light signals into neural signals, and transmit them to downstream neurons through the action of neurotransmitters, and finally cause corresponding behavioral responses. Therefore, it is of great significance for understanding the working principle of the visual system of Drosophila and exploring the regulation mechanism of its visual behavior.

1.2.3 Regulators

The regulatory protein is critical for the proper functioning of the visual transduction pathway. In Drosophila, there are many regulatory proteins, including Gq protein, Trp protein, InaD protein, PKC protein and so on.

Phototransduction is an important process in the visual system that converts light signals into neural responses. In Drosophila, phototransduction occurs within the rods of the compound eye and involves the response of the G protein-coupled receptor (GPCR) Rhodopsin1 (Rh1) to light activation. Subsequently, this leads to the activation of the G protein Gq and phospholipase C (PLC). PLC hydrolyzes phosphatidylinositol 4, 5-bisphosphate (PIP2) to generate two second messengers, diacylglycerol (DAG) and inositol 1,4, 5-triphosphate (IP3), which initiate a series of downstream signaling events culminate in the closure of photoreceptor ion channels at the photoreceptor cell membrane. However, the speed and sensitivity of this process need to be tightly regulated, and the regulator of G protein signaling (RGS) plays a key role in this regulation.

When the pigment-binding protein-opsin complex is formed, this complex activates downstream secondary signaling pathways. Wherein, G protein-coupled receptor signaling pathway refers to the interaction between G protein-coupled receptors on the membrane where opsin and opsinoids are located and G protein. When opsins or opsins change, their binding affinity to G protein-coupled receptors also changes, thereby affecting the activity of G proteins. These changes will subsequently cause a series of reactions, including activation of adenylyl acylase, activation of phosphatidylinositol pathway, etc (Palczewski, 2006).

G protein signaling regulator proteins play key regulatory roles in Drosophila's phototransduction. In Drosophila, six RGS proteins have been identified: RGS1, RGS2, RGS3, RGS4, RGS5 and CG5036. Among them, RGS1 and RGS9-1 have been shown to be involved in the rapid shutdown and recovery of light responses by accelerating the GTPase activity of Gαq and Gαi, respectively (Lee et al., 2015). RGS proteins are negative regulators of G protein signaling that accelerate the intrinsic GTPase activity of activated Gα subunits, thereby promoting G protein deactivation.

RGS1 is the first RGS protein found to be involved in Drosophila's phototransduction. It is predominantly expressed in photoreceptor cells and is required to quickly turn off the light response. RGS1 acts by accelerating the GTPase activity of Gαq, thereby terminating the activation of PLCβ and limiting the production of second messengers.

RGS9-1 is another RGS protein thought to be involved in the regulation of phototransduction in Drosophila. It is mainly expressed in cells surrounding photoreceptors and is required to restore the light response. RGS9-1 works by accelerating the GTPase activity of Gαi, thereby terminating the inhibition of phosphodiesterase (PDE), an enzyme that hydrolyzes cyclic guanosine monophosphate (cGMP), a light-sensitive enzyme that turns on photoreceptor cell membranes.

In addition to RGS proteins, phototransduction regulation also involves other related proteins. Among them, Rhodopsin kinase (Rh1K) is a kinase that plays an important role in phototransduction. This enzyme phosphorylates the Rh1 receptor and promotes its internalization and degradation, thereby limiting the duration of the light response (Kristaponyte et al., 2012).

Arrestins are a class of proteins that bind to G protein-coupled receptors and prevent their further activation. In Drosophila's phototransduction, two distinct arrestins have been identified: visual arrestin1 (Arr1) and Arr2. Both proteins bind to the Rh1 receptor and participate in its internalization and degradation (Kristaponyte et al.,

2012).

INAD protein (Inactivation No Afterpotential D) also plays an important role in Drosophila's phototransduction. It facilitates the transmission of visual signals by assembling into optical signaling complexes. This complex includes proteins such as Rh1, PLC, PDE, and TRP, which work together to convert light signals into neural signals (Tsunoda and Zuker, 1999).

Guanylate cyclase is an enzyme that synthesizes cyclic guanosine monophosphate (cGMP) into cyclic guanosine monophosphate (cGMP), a second messenger that opens light-sensitive channels in the membrane of Drosophila's photoreceptors. In photoreceptor cells, Gyc76C is considered to be one of the key enzymes for the synthesis and regulation of cGMP levels (Hardie and Raghu, 2001).

1.2.4 Transporters

Transporters in the Drosophila's visual system refer to membrane proteins involved in signal transduction during photoreception. These proteins mainly function to transfer ions and small molecules from one cell area to another so that neurons can receive the correct signals. One of the most representative proteins is the ion channel proteins (Ion channels). Ion channel proteins in the Drosophila's visual system include TRP (transient receptor potential), TRPL (TRP-like) and TRPγ, which are considered to be important molecules in the process of visual transduction (Niemeyer et al., 2001). These ion channel proteins are located on Drosophila's retinal pigment cells. When light stimulates the retina, the signal transduction pathway in pigment cells is activated, which triggers the opening and closing of ion channel proteins, regulates the ion concentration in retinal pigment cells, and then triggers signal transmission and neuronal excitation or inhibition (Wang and Montell, 2007; Montell, 2012).

In Drosophila's photoreceptor neurons, the carcinine transporter, CarT, is required to sustain histamine recycling (Stenesen et al., 2015; Xu et al., 2015; Chaturvedi et al., 2016).

TRP channels play a key role in visual transduction in Drosophila. At low light intensities, TRP channels open and allow calcium ions to flow into the retinal pigment cells, triggering the firing of the neurons. Opening of TRP channels also leads to opening of TRPL channels, which further enhances signaling. The TRPγ channel is only activated under high light intensity, and plays a role in inhibiting the TRP channel and TRPL channel, thereby preventing the signal from being over-amplified (Hardie and Franze, 2012).

In addition to triggering neural signal transduction, transporters in the Drosophila's visual system are also involved in the transport and metabolic regulation of substances, such as vitamin A metabolism and ATP synthesis. Among them, reverse saturated transfer protein (CRBP) complexes retinol with fatty acids for subsequent transport. Intracellular transport proteins (RBPs) help retinol enter the blood circulation (Blaner et al., 1994). ABCA4 is an ATP-binding cassette transporter located on the outer retinal segment that clears light-activated retinal out of the pigment epithelium to avoid toxic damage. Transporters such as NINAE, CINPA1, Atpα are also involved in the normal function of the Drosophila's visual system from the perspective of ATP synthesis and regulation.

1.3 Significance and content of present research

Vision is one of the important perception methods for Drosophila's behavioral response. Analyzing the Drosophila's visual protein network is of great significance for understanding the mechanism of insect vision, exploring vision-related human diseases, and developing new therapeutic methods. Drosophila perceives changes in environmental light through the opsin in the retina and transmits it to downstream neurons for visual information processing and behavioral responses. Therefore, the study of various proteins involved in the visual transmission process of Drosophila, such as opsins, G proteins, ion channels and transcription factors, can provide insight into the visual perception mechanism of Drosophila, and also help to reveal the visual mechanism of other animals.

Interaction networks are powerful tools to describe biological interactions (Kuang and Zhang, 2011; Huang and Zhang, 2012; Li and Zhang, 2013; Xin and Zhang, 2020, 2021; Yang and Zhang, 2022; Zhang and Zhang, 2019; Zhang, 2011, 2012a-c, 2014, 2016, 2018; Zhang and Zhang Huang, 2023; Zhang and Qi, 2023). By constructing a protein-protein interaction network, the interaction relationship between proteins can be comprehensively analyzed, and the crucial proteins and complexes can be mined. Currently, large-scale analysis and prediction of protein function and its role in visual transmission has become possible. In view of the problems of time-consuming, high investment and low efficiency in traditional protein function's identification methods and crucial protein identification methods, big data analysis methods based on interaction networks are becoming a new type of effective means.

The present study uses the network biology method to study the protein-protein interactions of Drosophila's visual system as a whole, describes proteins and predicts potential crucial proteins through the network, and lays the foundation for further exploration of the molecular mechanism of Drosophila's vision. Meanwhile, this research is also expected to provide reference and enlightenment for the research of other insect vision or animal perception mechanisms.

2 Materials and Methods

2.1 Data collection of visual proteins

PubMed (https://pubmed.ncbi.nlm.nih.govl) is a free literature database provided by the National Library of Medicine (National Library of Medicine), which includes journal articles and conferences in the field of biomedicine and life sciences papers, newspaper articles, etc. The FlyBase database (https://flybasc.org/) is a comprehensive Drosophila genomics database, which contains the genetic information, molecular biological information and biochemical information of the similar model organism Drosophila, and is the same as NCBI already done linking. In this study, by searching keywords related to Drosophila vision, such as Drosophila visual proteins, Drosophila opsin, Drosophila rhodopsin, etc., in the published literature, the visual organs expressed in the visual organ of Drosophila and sensitive to vision were selected. System-associated proteins serve as seed proteins.

2.2 Functional Gene Ontology Enrichment Analysis

GO enrichment analysis (Gene Ontology Enrichment Analysis) is a commonly used bioinformatics analysis method, which can be used to systematically annotate and classify the list of genes or proteins, and evaluate the relationship between these genes or proteins and specific biological processes, cellular components and correlation of molecular functions (Ashburner et al., 2000). Specifically, the method uses statistical methods to compare the list of genes or proteins to be analyzed with a preset gene ontology (Gene Ontology, GO) to determine the enrichment degree of certain GO terms in the gene set to be analyzed. In this process, genes are usually annotated into different types: Molecular Function (MF): describe the biological activity exhibited by the gene-encoded protein, such as catalyzing reactions, binding molecules or regulating cell signals; cell Component (Cellular Component, CC): describes the location of the gene-encoded protein, such as cell membrane, mitochondria, ribosome, etc.; Biological Process (Biological Progress, BP): describes the biological process that the gene participates in, such as immune response, metabolic pathway, cell cycle, etc. (Ashburner et al., 2000).

We used Rstudio and added the clusterProfiler package to perform GO enrichment analysis on visual genes (Yu et al., 2012). The package's easy-to-use interface and complete, efficient visualization help to improve the accuracy and reliability of GO enrichment.

2.3 Construction of protein-protein interaction network of visual system in Drosophila

Networks of protein-protein interactions (PPIs) are used to represent the interactions between proteins in living

organisms. Based on graph theory, the nodes in the protein interaction network represent proteins, and the edges connecting two nodes represent the interactions between the corresponding two proteins (von Mering et al., 2002; Huang and Zhang, 2012; Li and Zhang, 2013; Xin and Zhang, 2020, 2021; Yang and Zhang, 2022; Zhang and Zhang, 2019; Zhang, 2012a, 2014, 2016, 2018; Zhang and Huang, 2023). We uses the STRING database (https://string-db.org/) to query PPIs, which covers more than 2,000 different biological species worldwide, and integrates data from public databases and high-throughput experimental techniques such as yeast two-hybrid , mass spectrometry, and structural biology data.

The confidence range of the interaction relationship in the STRING database is: <0.4 is low confidence, 0.4-0.7 is medium confidence, and >0.7 is high confidence (von Mering et al., 2005; Xin and Zhang, 2020, 2021; Yang and Zhang, 2022; Zhang and Zhang, 2019). In this study, the obtained seed proteins were entered into the STRING database, and the interacting proteins and PPIs from all sources in the database were obtained with a confidence level of 0.4, which is the most commonly used analysis standard for the STRING database.

3 Results and Analysis

3.1 GO enrichment analysis

The clusterProfiler package was used to perform GO enrichment analysis on visual proteins in the network, and the enrichment results with P.adjust≤0.05 and GO level>5 were selected, and a total of 61 terms were obtained, including 32 BPs, 18 CCs, and 11 MEs. BP showed that these genes play an important role in biological rhythm, morphogenesis and basic metabolism. The most enriched biological processes were locomotor rhythm and compound eye morphogenesis. Phosphatidylinositol phosphorylation and cell-cell adhesion were also highly enriched. The results of CC analysis showed that these genes were mainly located in the cytoplasm (cytoplasm) and in various complexes. In MF, the significantly enriched term is protein binding, and the remaining terms are mostly related to the regulation of proteases (Table 1, Fig. 1).

3.2 Protein-protein interaction network of visual system

In present study, 52 visual proteins were used as seed proteins (Table 2), and the protein-protein interaction network of Drosophila's visual system was constructed through the STRING database, and the network visualization was realized by Cytoscape. This network contains a total of 248 proteins (Table 3) and 2948 interactions (Fig. 2; Table 4, see supplementary material for details).

The values of degree centrality (Li and Zhang, 2013; Xin and Zhang, 2020, 2021; Yang and Zhang, 2022; Zhang and Zhang, 2019; Zhang, 2016, 2018; Zhang and Huang, 2023) of visual proteins showed that Akt1 (93), arm (81), Src42A (78), Pten (73), Rho1 (73), norpA (73), and Egfr (71), etc., are the most important or crucial visual proteins in Drosophila, while CG11674 (2), CG13606 (2), CG9317 (2), dpr11 (2), ort (2), CG14521 (1), and eap (1), etc., are the least important or crucial visual proteins in Drosophila (Table 5).

Table 1 The results of the gene ontology enrichment analysis of visual proteins in Drosophila (top 10).

ID	Description	Gene Ratio	P.adjust	count	Genes
BP					
GO:0045475	locomotor rhythm	10/124	1.26E-05	10	DCO, NEJ, DLG1, CLK, E, CKIIALPHA, TIM, PER, VRI, SXC
GO:0001745	compound eye morphogenesis	12/124	1.26E-05	12	KLAR, NEJ, RST, EX, SHG, OC, HBS, DSH, SNS, P120CTN, LAM, PYD
GO:0046854	phosphatidylinositol phosphorylation	8/124	1.30E-05	8	FWD, PI3K59F, PIP4K, IPP, FAB1, IP3K2, IP3K1, PI4KIIIALPHA
GO:0098609	cell-cell adhesion	9/124	1.49E-05	9	DLG1, RST, SHG, ALPHA-CAT, HBS, ZYX, SNS, P120CTN, PYD
GO:0007623	circadian rhythm	8/124	4.53E-05	8	DCO, NORPA, CLK, E, CKIIALPHA, CWO, PER, VRI
GO:0046488	phosphatidylinositol metabolic process	5/124	9.97E-05	5	NORPA, SKTL, PIP5K59B, PIP4K, FAB1
GO:0007165	signal transduction	17/124	9.97E-05	17	CG30054, RHOGAPP190, GALPHAO, GPRK1, GALPHAQ, CG31140, S6K, RDGA, OCRL, GALPHAI, ORT, DCO, NORPA,
GO:0043052	thermotaxis	6/124	9.97E-05	6	DLG1, WDB, CG32568, GR28B ORT, NORPA, GALPHAQ, PLE, RDGA, NINAE
GO:0045880	positive regulation of smoothened signaling pathway	8/124	9.97E-05	8	GPRK1, DCO, NEJ, WDB, PKA-R1, CKIIALPHA, PAR-6, PI4KIIIALPHA
GO:0032922	circadian regulation of gene expression	5/124	2.03E-04	5	NEJ, CLK, PHR6-4, CWO, PER
CC					
GO:0005737	cytoplasm	57/124	5.41E-10	57	RUMP, VINC, GPRK1, CLK, FKBP59, PP2A-29B, FWD, SC35, ALPHA-CAT, DSH, IP3K2, LFT, IP3K1, CUP, GCKIII, CG31140, PI3K59F, OCRL, DCO, NOS, CG2104, CG9578, NUMB, NINAC, PP1-87B, RL, APLIP1, NINAA, STRIP, L(2)GL, VELI, E, PLE, FLW, MSP300, TANT, CKA, P120CTN, PI4KIIIALPHA, MBS, PHR6-4, PKA-R1, CKIIBETA2, OSK, POLO, CKIIALPHA, PUM, S6K, PP4-19C, KST, KLAR, MYPT-75D, TIM, LAM, PER, CG8509
GO:0000159	protein phosphatase type 2A complex	7/124	8.06E-08	7	PP2A-29B, CG4733, CG2104, WDB, CG32568, CG8509, TAP42
GO:0090443	FAR/SIN/STRIPAK complex	6/124	7.48E-07	6	PP2A-29B, STRIP, SLMAP, CKA,

					CCM3, FGOP2
GO:0016324	apical plasma membrane	11/124	8.15E-06	11	RST, SHG, SKTL, HBS, SNS, LFT, GALPHAI, BAZ, PAR-6, KST, EGFR
GO:0005938	cell cortex	11/124	9.13E-06	11	DLG1, L(2)GL, SHG, OSK, SKTL, MTM, NUMB, GALPHAI, BAZ, PAR-6, CHC
GO:0005912	adherens junction	8/124	4.06E-05	8	VINC, RST, SHG, ALPHA-CAT, HBS, P120CTN, PYD, BAZ
GO:0016027	inaD signaling complex	5/124	5.23E-05	5	NORPA, GALPHAQ, FKBP59, NINAC, NINAE
GO:0048471	perinuclear region of cytoplasm	9/124	8.47E-05	9	KLAR, DLG1, MSP300, NOS, KOI, PLE, TIM, PER, CHC
GO:0005634	nucleus	48/124	1.46E-04	48	RUMP, B, CLK, SRP54, VRI, FLW, NONA, SC35, WDB, TANT, OC, DSH, CKA, P120CTN, IP3K2, PNUTS, CWO, CG32568, IP3K1, CUP, XBP1, PHR6-4, CG31140, PPH13, CKIIALPHA, POLO, SSU72, PUM, S6K, PP4-19C, PAR-6, DCO, NEJ, CG2104, NOS, NUMB, NINAC, TIM, PP1-87B, LAM, RBF2, RL, TIMEOUT, PER, X16, CG8509, ATF6, SF2
GO:0005911	cell-cell junction	6/124	7.99E-04	6	RST, EX, VELI, HBS, ZYX, SNS
MF					
GO:0005515	protein binding	39/124	1.07E-09	39	GALPHAO, CLK, FKBP59, MTM, GALPHAI, EGFR, MSP300, SHG, ALPHA-CAT, DSH, CKA, SNS, CUP, LIPRIN-ALPHA, CKIIALPHA, POLO, S6K, PAR-6, KST, DCO, KLAR, NEJ, DLG1, EX, NOS, SKTL, ZYX, NUMB, NINAC, TIM, PP1-87B, LAM, RBF2, NINAE, APLIP1, BAZ, PER, SF2, CHC
GO:0019888	protein phosphatase regulator activity	6/124	2.30E-05	6	PP2A-29B, CG4733, WDB, MYPT-75D, CG32568, TAP42
GO:0019901	protein kinase binding	9/124	4.71E-05	9	STRIP, MSP300, L(2)GL, SLMAP, CKA, CCM3, RL, APLIP1, MBS
GO:0016301	kinase activity	9/124	1.97E-04	9	FWD, CG31140, PI3K59F, CKA, RDGA, IP3K2, IP3K1, PI4KIIIALPHA, EGFR
GO:0003729	mRNA binding	11/124	0.003957108	11	RUMP, NONA, NOS, SC35, OSK, SRP54, PUM, NIPP1, X16, SF2, CUP
GO:0008134	transcription factor binding	7/124	0.0083886	7	NEJ, EX, CLK, TIM, RBF2, RL, PER
GO:0001664	G-protein coupled receptor	5/124	0.01072362	5	CG30054, GPRK1, GALPHAO,

	binding		6		GALPHAQ, GALPHAI
GO:0004712	protein serine/threonine/tyrosine kinase activity	8/124	0.011400021	8	DCO, CKIIALPHA, POLO, PEK, NINAC, S6K, RL, EGFR
GO:0004672	protein kinase activity	10/124	0.016981416	10	GCKIII, GPRK1, DCO, CKIIALPHA, POLO, PEK, NINAC, S6K, RL, EGFR
GO:0004674	protein serine/threonine kinase activity	9/124	0.016981416	9	GCKIII, GPRK1, DCO, CKIIBETA2, CKIIALPHA, POLO, NINAC, S6K, RL

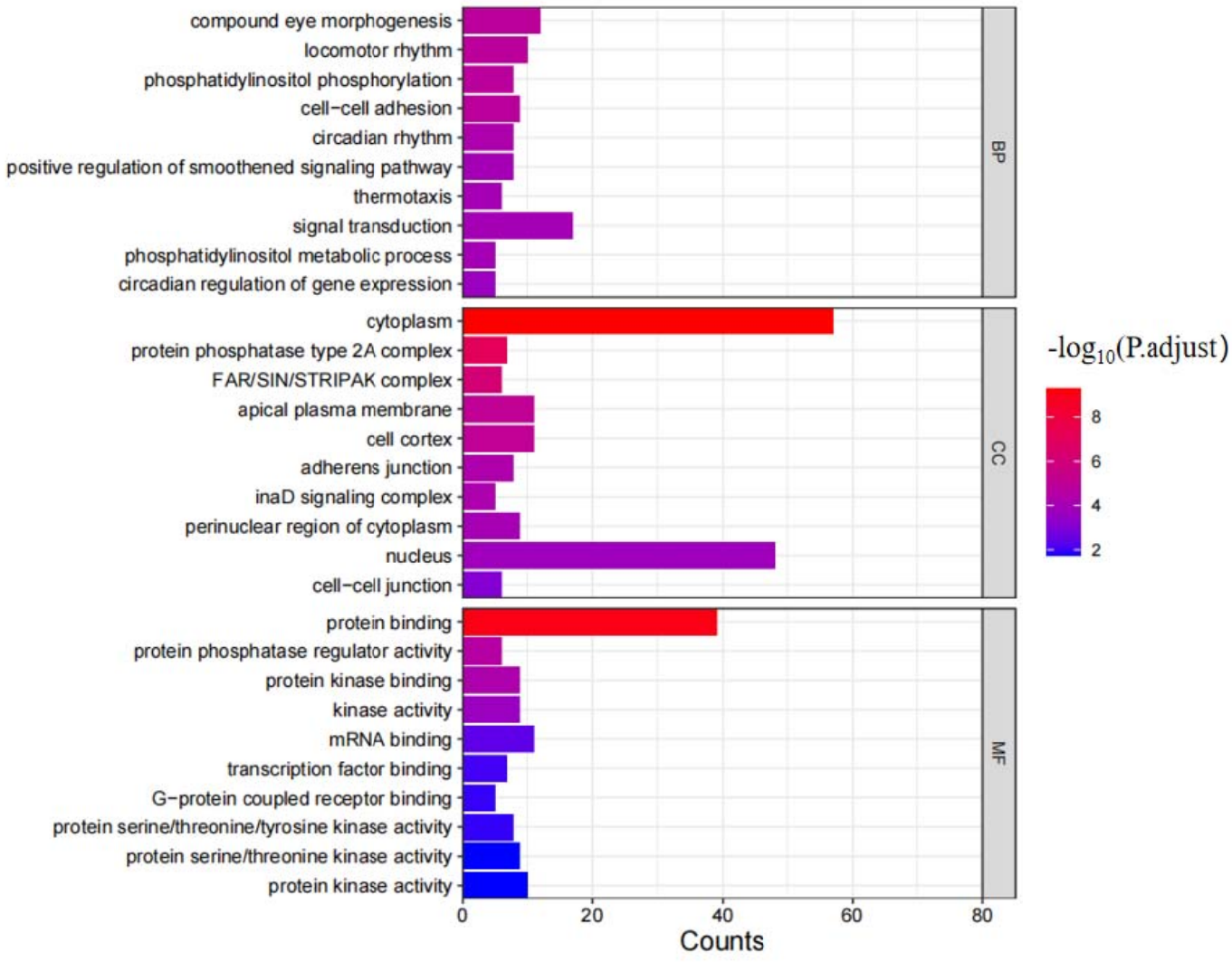

Fig. 1 Histograms of GO terms enriched in visual proteins in Drosophila (top 10). Colors indicate P.adjust. The abscissa is the number of genes associated with the term in the related genes.

Table 2 52 seed proteins related to visual functions in Drosophila.

Name	Fbid-key	Symbol	Protein
CarT	FBgn0032879	CarT	Carcinine transporter
CK2	FBgn0026136	CkIIbeta2	Casein kinase II beta2 subunit
Clk	FBgn0023076	Clk	Clock
crb	FBgn0259685	crb	crumbs
cyc	FBgn0023094	cyc	cycle
dpr11	FBgn0053202	dpr11	defective proboscis extension response 11
ebony	FBgn0017833	Dtrv\ebony	ebony
p120ctn	FBgn0260799	p120ctn	p120 catenin
eyes	FBgn0031414	eyes	eyes shut
Hdc	FBgn0005619	Hdc	Histidine decarboxylase
heca	FBgn0010113	heca	headcase
HisCl1	FBgn0037950	HisCl1	Histamine-gated chloride channel subunit 1
Ine	FBgn0011603	ine	inebriated
Rst	FBgn0003285	rst	roughest
Klar	FBgn0001316	klar	klarsicht
Koi	FBgn0265003	koi	klaroid
shg	FBgn0003391	shg	shotgun
ninaA	FBgn0002936	ninaA	neither inactivation nor afterpotential A
ninaB	FBgn0002937	ninaB	neither inactivation nor afterpotential B
ninaC	FBgn0002938	ninaC	neither inactivation nor afterpotential C
ninaE	FBgn0002940	ninaE	neither inactivation nor afterpotential E
norpA	FBgn0262738	norpA	no receptor potential A
Nos	FBgn0011676	Nos	Nitric oxide synthase
Ort	FBgn0003011	ort	ora transientless
Oc	FBgn0004102	oc	ocelliless
PLc	FBgn0004611	Plc21C	Phospholipase C at 21C
Pp2A	FBgn0260439	Pp2A-29B	Protein phosphatase 2A at 29B
Pph13	FBgn0023489	Pph13	PvuII-PstI homology 13
Rh2	FBgn0003248	Rh2	Rhodopsin 2
Rh3	FBgn0003249	Rh3	Rhodopsin 3
Rh4	FBgn0003250	Rh4	Rhodopsin 4
Rh5	FBgn0014019	Rh5	Rhodopsin 5
Rh6	FBgn0019940	Rh6	Rhodopsin 6
Sac1	FBgn0283500	Sac1	Sac1 phosphatase
sdk	FBgn0021764	sdk	sidekick

tant	FBgn0028980	tant	tantalus
trpl	FBgn0005614	trpl	transient receptor potential-like
nonA	FBgn0004227	nonA	no on or off transient A
Arr1	FBgn0000120	Arr1	Arrestin 1
Arr2	FBgn0000121	Arr2	Arrestin 2
Gr28b	FBgn0045495	Gr28b	Gustatory receptor 28b
Rdh1	FBgn0033205	Rdh1	Retinol dehydrogenase 1
RBP1	FBgn0286124	Hsap\RBP1	retinol binding protein 1
Rbp	FBgn0262483	Rbp	RIM-binding protein
GstD1	FBgn0001149	GstD1	Glutathione S transferase D1
GstD5	FBgn0010041	GstD5	Glutathione S transferase D5
Crc	FBgn0000370	crc	cryptocephal
Best3	FBgn0036492	Best3	Bestrophin 3
inaD	FBgn0001263	inaD	inactivation no afterpotential D
inaC	FBgn0004784	inaC	inactivation no afterpotential C
Flw	FBgn0000711	flw	flapwing
Pka	FBgn0000489	Pka-C3	Protein kinase, cAMP-dependent, catalytic subunit 3

Table 3 248 visual proteins in Drosophila.

Name	Fbid-key	Protein
alpha-Cat	FBgn0010215	alpha Catenin
aPKC	FBgn0261854	atypical protein kinase C
Aplip1	FBgn0040281	APPL-interacting protein 1
AKT1	FBgn0287911	AKT serine/threonine kinase 1
arm	FBgn0000117	armadillo
Arr1	FBgn0000120	Arrestin 1
Arr2	FBgn0000121	Arrestin 2
Atf6	FBgn0033010	Atf6
aub	FBgn0000146	aubergine
Axn	FBgn0026597	Axin
b	FBgn0000153	black
baz	FBgn0000163	bazooka
Best3	FBgn0036492	Bestrophin 3
brp	FBgn0259246	bruchpilot
cac	FBgn0263111	cacophony
CadN	FBgn0015609	Cadherin-N
Cam	FBgn0000253	Calmodulin
CaMKII	FBgn0264607	Calcium/calmodulin-dependent protein kinase II
CarT	FBgn0032879	Carcinine transporter
Ccm3	FBgn0038331	Cerebral cavernous malformation 3
CG10426	FBgn0036273	Inositol polyphosphate 5-phosphatase E
CG2104	FBgn0037365	-
CG2929	FBgn0037339	Phosphatidylinositol 4-kinase II alpha
CG30054	FBgn0050054	-
CG31140	FBgn0051140	-
CG32568	FBgn0052568	-
CG3530	FBgn0028497	Myotubularin related protein 6
CG3793	FBgn0028507	-
CG4733	FBgn0038744	-
CG5068	FBgn0035951	-
CG8509	FBgn0030696	-
CG9578	FBgn0031094	-
Chc	FBgn0000319	Clathrin heavy chain
ci	FBgn0004859	cubitus interruptus
CK2	FBgn0264492	casein kinase IIalpha

Cka	FBgn0044323	Connector of kinase to AP-1
CkIIalpha	FBgn0264492	casein kinase Iialpha
CkIIbeta2	FBgn0026136	Casein kinase II beta2 subunit
Clk	FBgn0023076	Clock
cno	FBgn0259212	canoe
crb	FBgn0259685	crumbs
crc	FBgn0000370	cryptocephal
cry	FBgn0025680	cryptochrome
cu	FBgn0261808	curled
cup	FBgn0000392	cup
cwo	FBgn0259938	clockwork orange
cyc	FBgn0023094	cycle
dco	FBgn0002413	discs overgrown
dlg1	FBgn0001624	discs large 1
dpr11	FBgn0053202	defective proboscis extension response 11
dsh	FBgn0000499	dishevelled
Dsor1	FBgn0010269	Downstream of raf1
eap	FBgn0052099	-
ebony	FBgn0000527	ebony
Egfr	FBgn0003731	Epidermal growth factor receptor
eIF-2alpha	FBgn0261609	eukaryotic translation initiation factor 2 subunit alpha
Eip78C	FBgn0004865	Ecdysone-induced protein 78C
ex	FBgn0004583	expanded
ey	FBgn0005558	eyeless
fab1	FBgn0028741	fab1 kinase
Fgop2	FBgn0031871	Fibroblast growth factor receptor 1 oncogene partner 2
FKBP59	FBgn0029174	FK506-binding protein 59kD
flfl	FBgn0024555	falafel
flw	FBgn0000711	flapwing
fwd	FBgn0004373	four wheel drive
Gadd34	FBgn0034948	Protein phosphatase 1 regulatory subunit 15
Galphai	FBgn0001104	G protein alpha i subunit
Galphao	FBgn0001122	G protein alpha o subunit
Galphaq	FBgn0004435	G protein alpha q subunit
Gbeta76C	FBgn0004623	G protein beta-subunit 76C
GckIII	FBgn0266465	Germinal centre kinase III

Gprk1	FBgn0260798	G protein-coupled receptor kinase 1
Gr28b	FBgn0045495	Gustatory receptor 28b
GstD1	FBgn0001149	Glutathione S transferase D1
GstD10	FBgn0042206	Glutathione S transferase D10
GstD2	FBgn0010038	Glutathione S transferase D2
GstD4	FBgn0010040	Glutathione S transferase D4
GstD5	FBgn0010041	Glutathione S transferase D5
GstD7	FBgn0010043	Glutathione S transferase D7
GstD8	FBgn0010044	Glutathione S transferase D8
GstS1	FBgn0010226	Glutathione S transferase S1
Hakai	FBgn0032812	Hakai
hbs	FBgn0287864	hibris
hdc	FBgn0005619	Histidine decarboxylase
heca	FBgn0010113	headcase
Hel25E	FBgn0014189	Helicase at 25E
HisCl1	FBgn0037950	Histamine-gated chloride channel subunit 1
hth	FBgn0001235	homothorax
inaC	FBgn0004784	inactivation no afterpotential C
inaD	FBgn0001263	inactivation no afterpotential D
ine	FBgn0011603	inebriated
IP3K1	FBgn0032147	Inositol 1,4,5-triphosphate kinase 1
IP3K2	FBgn0283680	Inositol 1,4,5-triphosphate kinase 2
Ipk2	FBgn0031267	Inositol phosphate kinase 2
Ipp	FBgn0016672	Inositol polyphosphate 1-phosphatase
Itp-r83A	FBgn0010051	Inositol 1,4,5,-trisphosphate receptor
kibra	FBgn0262127	kibra
klar	FBgn0001316	klarsicht
koi	FBgn0265003	klaroid
ksr	FBgn0015402	kinase suppressor of ras
kst	FBgn0004167	karst
l(2)gl	FBgn0002121	lethal (2) giant larvae
Lam	FBgn0002525	Lamin
lft	FBgn0032230	lowfat
Liprin-alpha	FBgn0046704	Liprin-alpha
Mbs	FBgn0005536	Myosin binding subunit
Mob4	FBgn0259483	MOB kinase activator 4

Moe	FBgn0011661	Moesin
Msp300	FBgn0261836	Muscle-specific protein 300 kDa
mtm	FBgn0025742	myotubularin
mts	FBgn0004177	microtubule star
MYPT-75D	FBgn0036801	Myosin phosphatase targeting subunit 75D
N	FBgn0004647	Notch
nej	FBgn0261617	nejire
ninaA	FBgn0002936	neither inactivation nor afterpotential A
ninaB	FBgn0002937	neither inactivation nor afterpotential B
ninaC	FBgn0002938	neither inactivation nor afterpotential C
ninaE	FBgn0002940	neither inactivation nor afterpotential E
NiPp1	FBgn0026402	Nuclear inhibitor of Protein phosphatase 1
nonA	FBgn0004227	no on or off transient A
norpA	FBgn0262738	no receptor potential A
nos	FBgn0011676	Nitric oxide synthase
Not1	FBgn0085436	Not1
Numb	FBgn0002973	numb
oc	FBgn0004102	ocelliless
Ocrl	FBgn0023508	Oculocerebrorenal syndrome of Lowe
ort	FBgn0003011	ora transientless
Osbp	FBgn0020626	Oxysterol binding protein
osk	FBgn0003015	oskar
p120ctn	FBgn0260799	p120 catenin
Pak	FBgn0267698	p21-activated kinase
par-6	FBgn0026192	par-6
Patj	FBgn0067864	Patj
Pdk1	FBgn0020386	Phosphoinositide-dependent kinase 1
Pdp1	FBgn0016694	PAR-domain protein 1
PEK	FBgn0037327	pancreatic eIF-2alpha kinase
per	FBgn0003068	period
phr6-4	FBgn0016054	(6-4)-photolyase
Pi3K59F	FBgn0015277	Phosphatidylinositol 3-kinase 59F
Pi4KIIIalpha	FBgn0267350	Phosphatidylinositol 4-kinase III alpha
PIP4K	FBgn0039924	Phosphatidylinositol 5-phosphate 4-kinase
PIP5K59B	FBgn0034789	Phosphatidylinositol 4-phosphate 5-kinase 59B
Pis	FBgn0030670	Phosphatidylinositol synthase

Pka	FBgn0000273	Protein kinase, cAMP-dependent, catalytic subunit 1
Pka-C1	FBgn0000273	Protein kinase, cAMP-dependent, catalytic subunit 1
Pka-C3	FBgn0000489	Protein kinase, cAMP-dependent, catalytic subunit 3
Pka-R1	FBgn0259243	Protein kinase, cAMP-dependent, regulatory subunit type 1
Pka-R2	FBgn0022382	Protein kinase, cAMP-dependent, regulatory subunit type 2
Pkc53E	FBgn0003091	Protein C kinase 53E
PLc	FBgn0004177	microtubule star
Pld	FBgn0286511	Phospholipase D
ple	FBgn0005626	pale
PNUTS	FBgn0053526	Phosphatase 1 nuclear targeting subunit
polo	FBgn0003124	polo
Pp1-87B	FBgn0004103	Protein phosphatase 1 at 87B
Pp2A	FBgn0028980	tantalus
Pp2A-29B	FBgn0260439	Protein phosphatase 2A at 29B
PP2A-B	FBgn0042693	well-rounded
Pp4-19C	FBgn0023177	Protein phosphatase 19C
Pph13	FBgn0023489	PvuII-PstI homology 13
Pten	FBgn0026379	Phosphatase and tensin homolog
Ptpa	FBgn0016698	Phosphotyrosyl phosphatase activator
pum	FBgn0003165	pumilio
pyd	FBgn0262614	polychaetoid
Rac1	FBgn0010333	Rac1
Raf	FBgn0003079	Raf oncogene
Rbf	FBgn0015799	Retinoblastoma-family protein
Rbf2	FBgn0038390	Retinoblastoma-family protein 2
Rbp	FBgn0262483	RIM-binding protein
Rbp1	FBgn0260944	RNA-binding protein 1
Rbp2	FBgn0262734	eukaryotic translation initiation factor 4H1
rdgA	FBgn0261549	retinal degeneration A
RdgC	FBgn0265959	retinal degeneration C
Rdh1	FBgn0033205	Retinol dehydrogenase 1
Ref1	FBgn0010774	RNA and export factor binding protein 1
Rh2	FBgn0003248	Rhodopsin 2
Rh3	FBgn0003249	Rhodopsin 3
Rh4	FBgn0003250	Rhodopsin 4
Rh5	FBgn0014019	Rhodopsin 5

Rh6	FBgn0019940	Rhodopsin 6
Rh7	FBgn0036260	Rhodopsin 7
Rho1	FBgn0014020	Rho1
RhoGAPp190	FBgn0026375	Rho GTPase activating protein p190
Rim	FBgn0053547	Rab3 interacting molecule
rl	FBgn0003256	rolled
Rok	FBgn0026181	Rho kinase
Rop	FBgn0004574	Ras opposite
Rpt3	FBgn0028686	Regulatory particle triple-A ATPase 3
rst	FBgn0003285	roughest
rtp	FBgn0087005	retinophilin
rump	FBgn0267790	rumpelstiltskin
S6k	FBgn0283472	Ribosomal protein S6 kinase
Sac1	FBgn0283500	Sac1 phosphatase
sau	FBgn0267378	sauron
SC35	FBgn0265298	SR family splicing factor SC35
Scr	FBgn0003339	Sex combs reduced
scrib	FBgn0263289	scribble
sdk	FBgn0021764	sidekick
sds22	FBgn0028992	sds22
sdt	FBgn0261873	stardust
SF2	FBgn0283477	Splicing factor 2
shg	FBgn0003391	shotgun
Sir2	FBgn0038788	Sirtuin 2
Sk1	FBgn0030300	Sphingosine kinase 1
sktl	FBgn0016984	skittles
sl	FBgn0003416	small wing
Slmap	FBgn0040011	Sarcolemma associated protein
SmD1	FBgn0261933	Small ribonucleoprotein particle protein SmD1
SmD2	FBgn0261789	Small ribonucleoprotein particle protein SmD2
SmE	FBgn0261790	Small ribonucleoprotein particle protein SmE
SmF	FBgn0000426	Small ribonucleoprotein particle protein SmF
SmG	FBgn0016070	smaug
smo	FBgn0003444	smoothened
sna	FBgn0003448	snail
snRNP70K	FBgn0016978	small ribonucleoprotein particle U1 subunit 70K

sns	FBgn0024189	sticks and stones
sqh	FBgn0003514	spaghetti squash
SR3-9	FBgn0020238	14-3-3epsilon
Src42A	FBgn0264959	Src oncogene at 42A
Src64B	FBgn0262733	Src oncogene at 64B
Srp54	FBgn0024285	Splicing regulatory protein 54
Ssu72	FBgn0031054	Ssu72 CTD phosphatase
Strip	FBgn0035437	Striatin interacting protein
Su(H)	FBgn0004837	Suppressor of Hairless
Cry	-	-
sxc	FBgn0261403	super sex combs
Synj	FBgn0034691	Synaptojanin
tan	FBgn0028980	tantalus
Tap42	FBgn0051852	Two A-associated protein of 42kDa
tim	FBgn0014396	timeless
timeout	FBgn0038118	timeout
tra2	FBgn0003742	transformer 2
trp	FBgn0003861	transient receptor potential
trpl	FBgn0005614	transient receptor potential-like
tsh	FBgn0003866	teashirt
tws	FBgn0004889	twins
unc-13	FBgn0025726	unc-13
unk	FBgn0004395	unkempt
Vap-33A	FBgn0029687	VAMP-associated protein 33kDa
veli	FBgn0039269	veli
Vinc	FBgn0004397	Vinculin
vri	FBgn0016076	vrille
wdb	FBgn0027492	widerborst
wg	FBgn0284084	wingless
x16	FBgn0028554	x16 splicing factor
Xbp1	FBgn0021872	X box binding protein-1
yrt	FBgn0004049	yurt
Zyx	FBgn0011642	Zyxin

Table 4 Protein-protein interactions of visual system in Drosophila (in part; see supplementary material for details).

node1	node2	gene_fusion	phylogenetic_ cooccurrence	homology	coexpression	experimentally_determined _interaction	combined_ score
Akt1	alpha-Cat	0	0	0	0	0.051	0.478
Akt1	Rbf	0	0	0	0	0.085	0.555
Akt1	Ocrl	0	0	0	0	0.072	0.645
Akt1	Vinc	0	0	0	0.052	0.051	0.651
Akt1	N	0	0	0	0	0.396	0.904
Akt1	norpA	0	0	0	0	0.12	0.667
Akt1	sqh	0	0	0	0	0.085	0.491
Akt1	Moe	0	0	0	0.043	0.155	0.579
Akt1	Dsor1	0	0.414	0.625	0.052	0.207	0.621
Akt1	flw	0	0	0	0.052	0.146	0.644
Akt1	shg	0	0	0	0	0.05	0.797
Akt1	Egfr	0	0	0.548	0	0.153	0.698
Akt1	Pi3K59F	0	0	0	0.052	0.088	0.807
Akt1	Gadd34	0	0	0	0	0.047	0.449
Akt1	fwd	0	0	0	0.079	0.088	0.439
Akt1	Aplip1	0	0	0	0	0.293	0.819
Akt1	Rpt3	0	0	0	0	0.051	0.548
Akt1	dsh	0	0	0	0	0.097	0.815
Akt1	Sk1	0	0	0	0	0.049	0.47
Akt1	CG8509	0	0	0	0.052	0.12	0.502
Akt1	sl	0	0	0	0	0.42	0.897
Akt1	eIF-2alpha	0	0	0	0	0.047	0.562
Akt1	par-6	0	0	0	0.074	0.23	0.51
Akt1	cyc	0	0	0	0	0.069	0.599
Akt1	Gbeta76C	0.004	0	0	0.055	0.087	0.443
Akt1	CG10426	0	0	0	0	0.072	0.425
Akt1	Rh7	0	0	0	0	0.048	0.412
Akt1	Arr2	0	0	0	0	0.201	0.899
Akt1	Galphai	0	0	0	0	0.145	0.774
Akt1	ple	0	0	0	0	0	0.473
Akt1	Pp4-19C	0	0	0	0.048	0.087	0.61
Akt1	Ptpa	0	0	0	0.052	0.12	0.502
Akt1	smo	0	0	0	0.048	0.051	0.812
Akt1	Itp-r83A	0	0	0	0	0.12	0.694
Akt1	CG2104	0	0	0	0.052	0.12	0.502
Akt1	ksr	0	0	0.56	0	0.283	0.542
Akt1	PEK	0	0	0.555	0	0.066	0.419
Akt1	Lam	0	0	0	0.07	0.234	0.642
Akt1	wg	0	0	0	0.048	0.085	0.917
Akt1	mts	0	0	0	0.084	0.715	0.996
Akt1	FKBP59	0	0	0	0.052	0.229	0.6

Akt1	Sir2	0	0	0	0.052	0.075	0.911
Akt1	Su(H)	0	0	0	0.047	0.052	0.47
Akt1	sna	0	0	0	0	0.068	0.702
Akt1	Pp1-87B	0	0	0	0.1	0.146	0.679
Akt1	Rh6	0	0	0	0	0.048	0.413
Akt1	Rbf2	0	0	0	0	0.085	0.428
Akt1	ninaE	0	0	0	0	0.048	0.4
Akt1	l(2)gl	0	0	0	0.1	0.124	0.407
Akt1	Rh2	0	0	0	0	0.048	0.411
Akt1	crb	0	0	0	0	0.085	0.412
Akt1	CaMKII	0	0.392	0.655	0.095	0.055	0.416
Akt1	trp	0	0	0	0	0.048	0.431
Akt1	RhoGAPp190	0	0	0	0	0.044	0.446
Akt1	Arr1	0	0	0	0	0.201	0.448
Akt1	Atf6	0	0	0	0.09	0	0.476
Akt1	Pi4KIIIalpha	0	0	0	0.055	0.088	0.499
Akt1	fab1	0	0	0	0.052	0.05	0.502
Akt1	p120ctn	0	0	0	0	0.087	0.504
Akt1	GckIII	0	0	0.597	0.049	0.052	0.505
Akt1	Pld	0	0	0	0	0.054	0.521
Akt1	Eip78C	0	0	0	0	0.122	0.521
Akt1	tim	0	0	0	0	0	0.524
Akt1	Numb	0	0	0	0.073	0.092	0.542
Akt1	Galphaq	0	0	0	0.073	0.145	0.558
Akt1	pyd	0	0	0	0	0.046	0.593
Akt1	Xbp1	0	0	0	0	0	0.594
Akt1	scrib	0	0	0	0.09	0.072	0.595
Akt1	Cka	0	0	0	0.074	0	0.598
Akt1	Galphao	0	0	0	0	0.145	0.6
Akt1	rl	0	0.343	0.62	0.088	0.212	0.611
Akt1	CadN	0	0	0	0	0.05	0.665
Akt1	dlg1	0	0	0	0	0.251	0.703
Akt1	aPKC	0	0	0.811	0.056	0.411	0.704
Akt1	Pak	0	0	0.598	0.052	0.272	0.704
Akt1	ci	0	0	0	0.048	0.055	0.722
Akt1	Axn	0	0	0	0.047	0.091	0.769
Akt1	SR3-9	0	0	0	0.048	0.201	0.771
Akt1	Raf	0	0	0.559	0	0.458	0.817
Akt1	Src64B	0	0	0.56	0.052	0.208	0.867
Akt1	Cam	0	0	0	0	0.085	0.868
Akt1	Src42A	0	0.323	0.569	0.119	0.208	0.891
Akt1	Rho1	0	0	0	0.079	0.12	0.925
Akt1	nej	0	0	0	0	0.451	0.929
Akt1	Rac1	0	0	0	0.082	0.12	0.941

Akt1	CG32568	0	0	0	0.054	0.073	0.952
Akt1	Pp2A-29B	0	0	0	0.073	0.122	0.964
Akt1	PP2A-B	0	0	0	0.054	0.073	0.965
Akt1	S6k	0	0.438	0.851	0.595	0.528	0.994
Akt1	Pdk1	0	0	0.648	0.112	0.892	0.995
Akt1	arm	0	0	0	0.092	0.137	0.995
Akt1	wdb	0	0	0	0.102	0.874	0.996
Akt1	Pten	0	0	0	0.048	0.908	0.998
Aplip1	N	0	0	0	0	0	0.67
Aplip1	Src42A	0	0	0	0	0.079	0.413
Aplip1	Src64B	0	0	0	0	0.079	0.506
Aplip1	Rbp	0	0	0	0.104	0.96	0.977
Arr1	norpA	0	0	0	0.072	0	0.744
Arr1	Dsor1	0	0	0	0	0.05	0.739
Arr1	dsh	0	0	0	0.048	0.05	0.721
Arr1	Chc	0	0	0	0	0.635	0.861
Arr1	RdgC	0	0	0	0	0.051	0.718
Arr1	Gbeta76C	0	0	0	0.497	0.05	0.738
Arr1	Rh4	0	0	0	0.247	0.15	0.99
Arr1	Rh7	0	0	0	0	0.15	0.943
Arr1	Arr2	0	0	0.939	0.903	0.749	0.982
Arr1	Galphai	0	0	0	0.049	0.048	0.477
Arr1	Pph13	0	0	0	0.084	0	0.407
Arr1	smo	0	0	0	0	0.048	0.437
Arr1	ksr	0	0	0	0	0.08	0.633
Arr1	rtp	0	0	0	0.469	0	0.502
Arr1	ninaC	0	0	0	0.373	0	0.792
Arr1	Rh5	0	0	0	0.255	0.15	0.941
Arr1	ninaB	0	0	0	0.104	0	0.574
Arr1	Rh6	0	0	0	0.375	0.15	0.952
Arr1	Rh2	0	0	0	0.119	0.15	0.932
Arr1	ninaE	0	0	0	0.716	0.761	0.997
Arr1	Rh3	0	0	0	0.435	0.15	0.972
Arr1	trp	0	0	0	0.345	0	0.695
Arr1	Src42A	0	0	0	0	0.132	0.51

Table 5 Degree centrality of visual proteins in Drosophila.

ID	Protein	Degree	ID	Protein	Degree	ID	Protein	Degree	ID	Protein	Degree
1	Akt1	93	63	polo	31	125	Pkc53E	18	187	Msp300	10
2	arm	81	64	trp	31	126	Rbf	18	188	Not1	10
3	Src42A	78	65	CaMKII	30	127	eIF-2alpha	18	189	Pph13	10
4	Pten	73	66	cry	30	128	sds22	18	190	Rbp2	10
5	Rho1	73	67	cyc	30	129	Atf6	17	191	osk	10
6	norpA	73	68	per	30	130	Eip78C	17	192	ple	10
7	Egfr	71	69	sktl	30	131	Liprin-alpha	17	193	CG10915	9
8	wg	68	70	trpl	30	132	Mbs	17	194	Fgop2	9
9	Cam	66	71	Cka	29	133	Pka-C3	17	195	Mob4	9
10	Src64B	66	72	Patj	29	134	Rbp1	17	196	PEK	9
11	mts	65	73	Rh3	29	135	RhoGAPp190	17	197	Vap-33A	9
12	rl	65	74	Zyx	29	136	Slmap	17	198	ex	9
13	Rac1	63	75	CG2104	28	137	SmD1	17	199	Hakai	8
14	aPKC	62	76	CG8509	28	138	cac	17	200	IP3K1	8
15	dsh	61	77	Itp-r83A	28	139	x16	17	201	MYPT-75D	8
16	Pp2A-29B	59	78	PIP5K59B	28	140	CG3530	16	202	Rim	8
17	dlg1	55	79	Ptpa	28	141	CG3793	16	203	Scr	8
18	shg	55	80	ci	28	142	PIP4K	16	204	Srp54	8
19	N	54	81	fwd	28	143	Rop	16	205	Xbp1	8
20	Pp1-87B	54	82	inaC	28	144	SmF	16	206	CkIIbeta2	7
21	flw	53	83	CG32568	27	145	SmG	16	207	GstD1	7
22	sl	53	84	Pld	27	146	pum	16	208	GstD10	7
23	Galphai	51	85	Rh4	27	147	tra2	16	209	GstD2	7
24	Moe	51	86	Sir2	27	148	CG17760	15	210	GstD4	7
25	alpha-Cat	51	87	Synj	27	149	CG30054	15	211	GstD5	7
26	tws	50	88	sdt	27	150	CG42458	15	212	GstD7	7
27	Axn	46	89	Pdk1	26	151	Ref1	15	213	GstD8	7
28	Raf	46	90	ninaC	26	152	SC35	15	214	I-2	7
29	crb	46	91	CG11597	25	153	SmD2	15	215	PNUTS	7
30	dco	46	92	Pi3K59F	25	154	SmE	15	216	Rbp	7
31	par-6	45	93	Chc	24	155	Su(H)	15	217	crc	7
32	smo	45	94	Hel25E	24	156	hbs	15	218	e	7
33	Arr2	44	95	Rh5	24	157	mtm	15	219	hth	7
34	ninaE	44	96	Sac1	24	158	rst	15	220	ninaA	7
35	pyd	44	97	cno	24	159	snRNP70K	15	221	nos	7
36	Dsor1	43	98	kibra	24	160	sns	15	222	tsh	7
37	S6k	43	99	CG2929	23	161	vri	15	223	sau	7
38	baz	43	100	Clk	23	162	CG31140	14	224	Ipk2	6
39	Pp4-19C	42	101	Gadd34	23	163	Cry	14	225	aub	6
40	wdb	42	102	Ocrl	23	164	Lam	14	226	b	6
41	Galphaq	41	103	Pka-R1	23	165	Pdp1	14	227	cu	6
42	Pka-C1	41	104	RdgC	23	166	brp	14	228	Aplip1	5

43	Galphao	40	105	Rh2	23	167	rtp	14	229	Sk1	5
44	Rok	40	106	Tap42	23	168	NiPp1	13	230	sdk	5
45	SR3-9	40	107	sna	23	169	Strip	13	231	unk	5
46	p120ctn	39	108	veli	23	170	phr6-4	13	232	Ipp	4
47	scrib	39	109	CG4733	22	171	timeout	13	233	Koi	4
48	sqh	39	110	Rh7	22	172	Ccm3	12	234	Ssu72	4
49	CadN	38	111	ksr	22	173	FKBP59	12	235	cup	4
50	Gbeta76C	38	112	unc-13	22	174	Osbp	12	236	klar	4
51	Pak	37	113	Pis	21	175	cwo	12	237	Gr28b	3
52	Numb	36	114	Rpt3	21	176	yrt	12	238	HisCl1	3
53	Vinc	35	115	rump	21	177	CG9578	11	239	hdc	3
54	tim	35	116	GckIII	20	178	Rbf2	11	240	tan	3
55	PP2A-B	34	117	Gprk1	20	179	lft	11	241	ine	3
56	nej	34	118	SF2	20	180	ninaB	11	242	CG11674	2
57	CkIIalpha	33	119	fab1	20	181	nonA	11	243	CG13606	2
58	inaD	33	120	flfl	20	182	oc	11	244	CG9317	2
59	l(2)gl	33	121	Pka-R2	19	183	sxc	11	245	dpr11	2
60	Arr1	32	122	kst	19	184	CG5068	10	246	ort	2
61	Pi4KIIIalpha	32	123	rdgA	19	185	GstS1	10	247	CG14521	1
62	Rh6	31	124	CG10426	18	186	IP3K2	10	248	eap	1

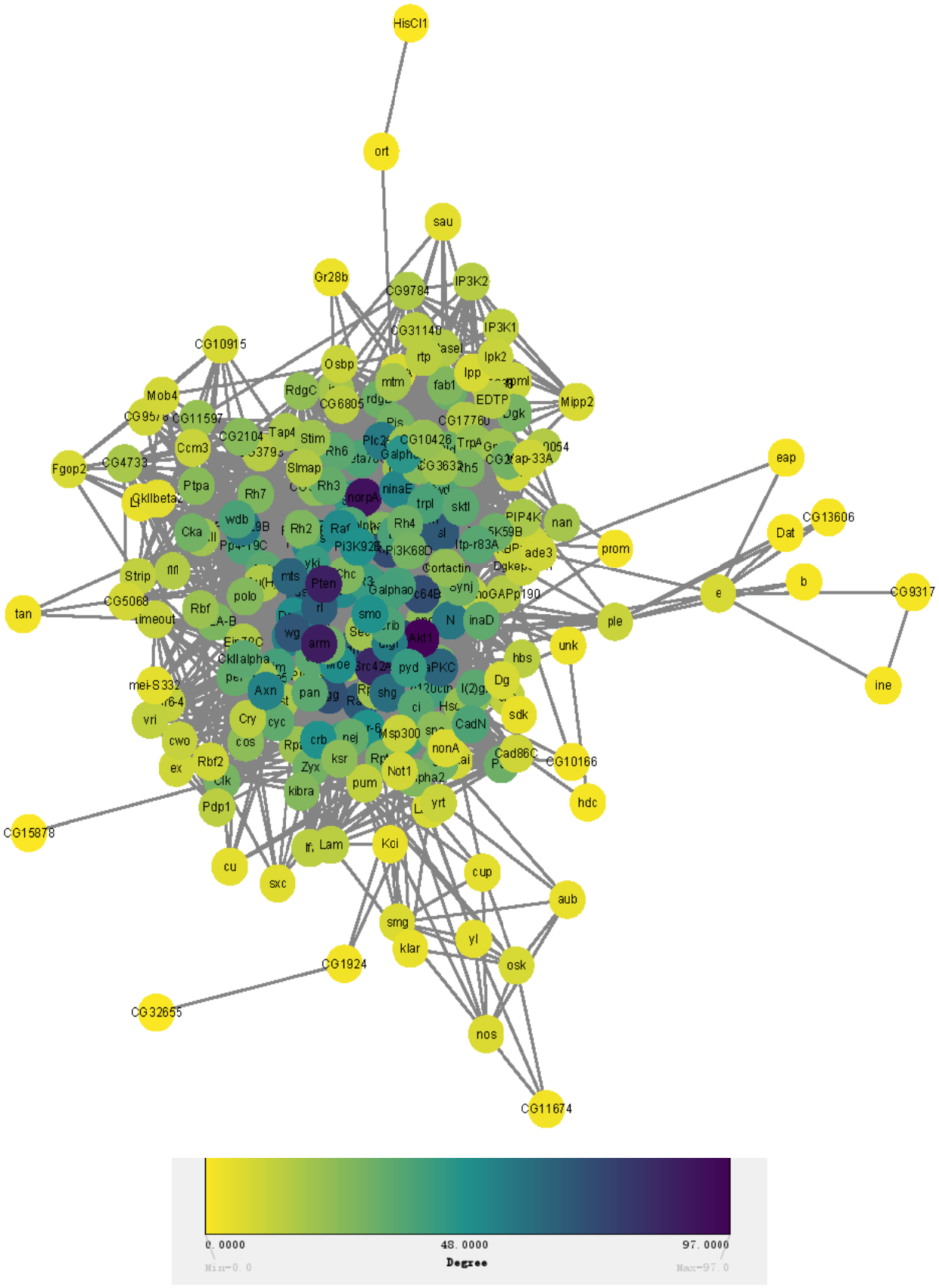

Fig. 2 The protein-protein interaction network of visual system in Drosophila. Proteins are represented by nodes, and protein-protein interactions are represented by the connection between nodes. The color is consistent with node degree.

4 Conclusions and Discussion

Degree centrality of visual proteins showed that Akt1, arm, Src42A, Pten, Rho1, norpA, and Egfr, etc., are the most important or crucial visual proteins in Drosophila. These proteins play an important role in the network structure. Among them, AKt1 has not been clearly confirmed that they directly affect the vision of Drosophila, but the important position of AKt1 in the network may mean that it has undiscovered visual influence, as a participatory protein kinases in various metabolic pathways and developmental processes (Mirth, 2012), may regulate the development of optic neurons in Drosophila like arm and Pten.

As an important regulatory gene for the development and function of the Drosophila's visual system, the EGFR gene has been widely discussed in many studies (Freeman, 1996). Specifically, mutations or deletions in the EGFR gene can lead to a reduction in the number of photoreceptor cells in the retina, or even a complete absence, resulting in the inability of fruitflies to perceive light. In addition, the regulation of the EGFR gene can also affect the proportion and location of various receptor cells in the retina, thereby affecting the sensitivity and positioning ability of Drosophila to light of different wavelengths and directions.

Another important one, Src42A gene encodes a tyrosine kinase, which affects the formation of eyes, neuron differentiation and synaptic plasticity. In the compound eye of Drosophila, each cell consists of 8 sensory cells and one pigment cell. Src42A gene can regulate the number and distribution of receptor cells in compound eyes, and then affect the structure and function of compound eyes. In addition, the Src42A gene is also involved in the differentiation and localization of retinal neurons, and participates in the differentiation of retinal neurons by regulating other molecules in the signaling pathway. Meanwhile, the Src42A gene also plays a key role in the formation of visual memory in Drosophila. Studies have shown that in learning process, the Src42A gene can regulate processes such as synaptic plasticity and neurotransmitter release, thereby affecting the visual learning and memory abilities of Drosophila.

Through GO enrichment analysis, Drosophila's visual proteins play an important role in biological rhythm, morphogenesis and basic metabolism. Among them, the enrichment degree was the highest in motor rhythm and compound eye morphogenesis. In addition, phosphatidylinositol phosphorylation and intercellular adhesion were also enriched at higher levels. The results of CC analysis showed that these genes were mainly localized in the cytoplasm and in various complexes. In MF, the enriched term is protein binding, and other terms are also involved in the regulation of proteases.

With the completion of biological genome sequencing and the increasing development and improvement of various protein databases, the use of network biology methods to study proteins will become a new direction of protein research (Huang and Zhang, 2012; Li and Zhang, 2013; Xin and Zhang, 2020, 2021; Yang and Zhang, 2022; Zhang and Zhang, 2019; Zhang, 2011, 2012a-c, 2014, 2016, 2018; Zhang and Zhang Huang, 2023; Zhang and Qi, 2023). In this study, based on the principle that interacting proteins have similar functions, the network biology method was used for the first time to construct and analyze the protein-protein interaction network of the visual system of Drosophila, in an attempt to discover more potential proteins involved in visual functions in a wider range. However, limited by the content of the search, the data are not enough to fully speculate on the potential crucial proteins in the existing proteins domains. Moreover, there are still some problems to be solved. For example, the analysis results are not fully confirmed by experimental data, and it needs to be verified by follow-up experiments.

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