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Genetics

# Photophobe (*Ppb*), a *Drosophila* mutant with a reversed sign of phototaxis; the mutation shows an allele-specific interaction with sevenless

(behavioral genetics/suppressor mutations/*Drosophila melanogaster*/photophobia/color-choice phototaxis)

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ABSTRACT **We have isolated a dominant behavioral mutation, Photophobe (*Ppb*), on the second chromosome of *Drosophila melanogaster*. Although wild-type flies are attracted towards green light, flies homozygous for the *Ppb* mutation avoid it over an intensity range of six logarithms. *Ppb* interacts in a dominant way with mutations in the sevenless (*sev*) gene, an X-chromosomal gene necessary for photoreceptor cell 7 differentiation in the *Drosophila* retina. Specific alleles of *sev* alter the *Ppb* behavioral phenotype; of eight *sev* alleles tested, two alleles enhanced the negative phototaxis of *Ppb*, whereas six alleles had the opposite effect. In no mutant combination of *Ppb* and *sev* was photoreceptor cell 7 restored. These data show that the *sev* gene, in addition to its role in the differentiation of photoreceptor cell 7, plays a role along with *Ppb* in a common visual information-processing pathway.**

Over 200 genes have been identified that have mutant phenotypes affecting development and function of the *Drosophila* visual system (1, 2). The defects of many nonphototactic mutants have been related to photoreceptor cell structure or the phototransduction process (3–5; for review, see ref. 2). Behavioral tests (6) and anatomical screens (7) have also led to the isolation of mutants with a range of visual-system defects (for example, see ref. 8). In one example, the double-mutant combination of reduced optic lobes (*rol*) and small optic lobes (*sol*) severely reduced the volume of the optic lobes to <12% normal. Such *rol sol* flies are nonresponsive to a rotating pattern of vertical light and dark stripes. However, they do tend to avoid a single, stationary or rotating stripe, whereas normal flies are attracted toward it (9, 10).

The sevenless (*sev*) gene is of particular interest because of the exquisite precision of its phenotype; each ommatidium in the adult compound eye of a *sev* mutant fly lacks one of the eight photoreceptors, photoreceptor cell 7 (R7). The normal *sev* gene product is necessary for the differentiation of cell R7 during early eye development (11–13). Flies carrying the *sev* mutation also have a behavioral abnormality. Wild-type flies, given a choice in a T maze between UV light and green light, show a 10-fold preference for phototaxis towards UV light. In the same test, *sev* mutant flies make the opposite choice, preferring green light (14, 15). This behavioral difference has been used to isolate new *sev* alleles (16, 17). We conjectured that the color-choice test could be used to find dominant extragenic suppressor mutations that would reverse the abnormal color preference of *sev* mutant flies. Such mutations might identify genes that interact with the *sev* gene during differentiation of R7 or that affect neuronal pathways that process visual information.

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In this paper, isolation and characterization of the mutation Photophobe (*Ppb*) is described. *Ppb* is a dominant mutation on chromosome 2 that was isolated on the basis of a reversal in the UV–green color preference of $sev^{LY3}$ flies. This change in behavior was not accompanied by the return of R7. Remarkably, flies carrying two copies of the Photophobe gene (*Ppb/Ppb*) are repelled from, rather than attracted toward light.

## MATERIALS AND METHODS

***Drosophila* Stocks.** Flies were raised on cornmeal-yeast-agar medium (18) at 25°C and 40% humidity in a 12-hr light/dark cycle. The stocks used in these studies were as follows: wild type (C-S, Canton-Special); $sev^{LY3}$ (11); $sev^{P3}$, $sev^{E1}$, $sev^{E4}$, $sev^{E5}$ (17); $sev^{d2}$, $sev^{f31E}$, $sev^{x3}$ (16). The mutations and balancer chromosomes used are described in Lindsley and Grell (1).

**Mutagenic Screen.** Males of the $sev^{LY3}$ strain were fed 25 mM ethylmethane sulfonate in 1% sucrose for 24 hr (19) and mated to $sev^{LY3}$ homozygous females. Sixty thousand progeny, 2–6 days old, were tested in groups of 50; each group was run through three trials of the T-maze photo-choice (green versus UV light) test. Individuals choosing UV light in all three choice trials were then tested for phototaxis toward an unfiltered germicidal lamp in a 15-trial countercurrent apparatus, and ones that moved toward UV light >7 of 15 times were used to establish 196 lines. Populations of these lines (all in $sev^{LY3}$ background) were tested for heritable alterations in color-choice behavior. Six lines that consistently showed preference for UV over green were then established, one of which ($sev^{LY3}$; *Ppb*/SM6a) was chosen for detailed analysis.

*Ppb* was maintained as a balanced stock (the double mutant—$sev^{LY3}$; *Ppb*/SM6a or the single mutant—*Ppb*/SM6a). For all experimental manipulations, females from these balanced stocks were outcrossed to $sev^{LY3}$ or C-S males, respectively. All phototaxis results reported are either for the $sev^{LY3}$; *Ppb*/+ or the *Ppb*/+ progeny. The original mutagenized second chromosome containing *Ppb* was a homozygous lethal mutation. In mapping the *Ppb* mutation, two useful recombinant chromosomes were obtained. One of these (*al dp b Bl, Ppb*) also carried a recessive lethal mutation. The other recombinant chromosome (*al dp b,Ppb*) did not contain a recessive lethal mutation, but the homozygous flies were not suitable for phototactic experiments because of their mutant wings (20, 21). To generate homozygous *Ppb* flies that were heterozygous for all other recessive mutations, lines containing each of these two recombinant chromosomes were separately interbred with the balanced line containing the original mutagenized chromosome, and all experiments

Abbreviation: R7, photoreceptor cell 7; C-S, Canton-Special wild type; I, light intensity.

were duplicated with both lines. Although *Ppb* was unambiguously assigned to the right arm of the second chromosome, determination of its precise location has proved difficult, possibly due to modifiers segregating in the stocks used thus far in mapping studies.

**Behavioral Characterization.** Phototactic and color-choice behavior were determined in a T maze (22) as diagramed in Fig. 1*A*. Unetherized flies in groups of 25–50 were adapted to room light for at least 30 min and were shaken from the start tube into a sliding chamber that was then moved into a central position between two 17 × 100-mm clear polystyrene test tubes (Falcon Plastics). In a darkened room the apparatus was placed at the center of a box, 21 cm on a side, lined with black felt, and each tube was separately illuminated from its far end through a portal. After 30 sec of free-running phototaxis with intermittent agitation by tapping the apparatus on a black rubber pad, the choice tubes were isolated from each other, and the flies in each tube were counted. In color-choice tests, green light was tested against UV, whereas in phototaxis tests, one light source was tested against darkness. Green illumination was through a 550-nm narrow-band interference filter with a 150-W fiber-optic source (model MK II, Ehrenreich Photo Optical Industries; Garden City, NY) set at maximum intensity. UV illumination was through a 350-nm narrow-band interference filter with a 25-W germicidal lamp. Relative intensities were controlled by interposition of Kodak Wratten neutral-density filters across the light path; the intensity without any neutral-density filter is taken as a standard (log I = 0). Light intensities were measured with a blue-enhanced silicon photodiode (type PIN-5DP/SB, United Detector Technology, Hawthorne, CA) and a picoammeter (model 485, Keithley Instruments, Cleveland, OH). At the central choice site of the T maze, with no neutral density filters in place (log I = 0), the green light flux was approximately 1 W/m$^2$, and the UV was approximately 1 mW/m$^2$. At the ends of the clear plastic tubes closest to the light sources, the intensities were an order of magnitude greater.

The results are reported as a phototactic index, $\lambda$: $\lambda(a/b) = (n_a - n_b)/(n_a + n_b)$ where $n_a$ is the number of flies in tube a, and $n_b$ is the number of flies in tube b. The few flies that sometimes remained in the central chamber were not counted. $\lambda = +1$ indicates that all the flies were attracted to light source a, $\lambda = -1$ indicates complete attraction to light source b, and $\lambda = 0$ indicates that the flies were divided equally between the two tubes. Mean values of $\lambda$ and standard errors of the mean (SEM) for at least three separate measurements are reported.

Countercurrent phototactic tests were done in a 15-trial countercurrent apparatus (21) with the use of either an unfiltered 15-W cool white fluorescent lamp or an unfiltered 25-W germicidal lamp at a distance of 20 cm from the bulb.

## RESULTS

**The Isolation of *Ppb*.** Phototaxis was measured in a T maze as shown in Fig. 1*A* (22). This test measures phototactic preference during an agitated-state escape response, which largely overrides other stimuli within the complex test environment (23). In phototaxis tests, one light source was tested against darkness; for color-choice tests, UV light was tested against green light. Tests in total darkness showed no inherent bias toward either direction in the apparatus.

When given a choice between UV light and green light, normal flies choose UV light, whereas $sev^{LY3}$ flies choose green light (9, 11); Fig. 1*B* describes this result. The Photophobe (*Ppb*) gene was isolated as a dominant mutation on chromosome 2 that causes a reversal in the color-choice behavior of $sev^{LY3}$ flies. That is, flies carrying both mutations ($sev^{LY3}$; *Ppb*/+) prefer UV light over green light (Fig. 1*B*).

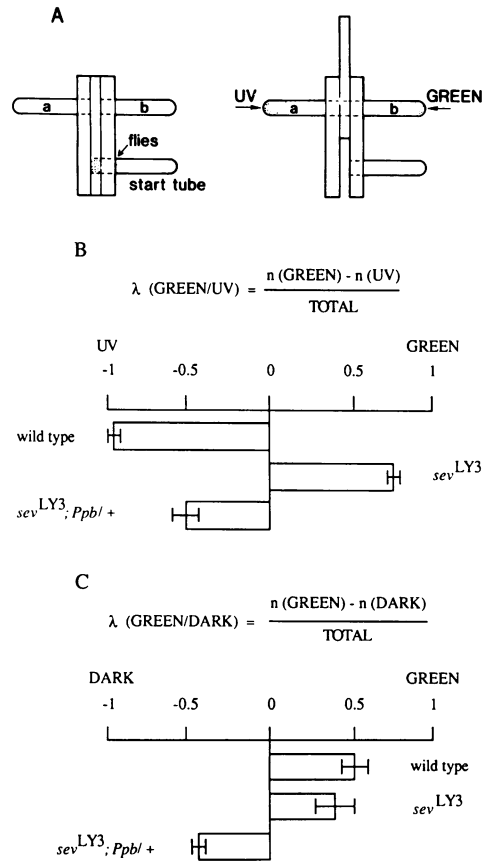


FIG. 1. Color-choice and phototactic response of normal and mutant flies. (*A*) T maze used for phototactic and color-choice tests. (*B*) Flies were tested for color-choice preference between 550-nm green light and 350-nm UV light (log $I_{green} = -1.5$; log $I_{UV} = 0$). (*C*) Flies were tested for phototactic preference between darkness and 550-nm green light (log $I_{green} = 1.5$). In this and in all other figures, the reported $\lambda$ indicates the mean of at least three independent measurements ± SEM. At least 300 6- to 8-day-old flies of each genotype were tested.

This effect is seen in spite of the continued absence of R7 in the eyes of the doubly mutant flies (data not shown). An unexpected finding was that, under defined conditions where both normal and $sev^{LY3}$ flies prefer green light over darkness, $sev^{LY3}$; *Ppb*/+ flies prefer darkness over green light (Fig. 1*C* and Table 1); hence, the designation of this mutation as Photophobe.

As an independent test of the negative phototaxis of $sev^{LY3}$; *Ppb*/+ flies, the countercurrent apparatus (21) was used (see text and Fig. 2). When given 15 consecutive trials of phototaxis towards visible light, normal flies chose light over darkness an average of 13 of 15 times. In contrast, $sev^{LY3}$; *Ppb*/+ flies chose light <2 of 15 times (Fig. 2*A*). When tested in the countercurrent apparatus for movement away from light, normal flies avoided light an average of only 3–4 of 15 trials. In contrast, $sev^{LY3}$; *Ppb*/+ flies avoided light an average of 12–13 of 15 trials (Fig. 2*B*). This observation demonstrates a true photophobic response; the poor response toward light cannot be ascribed to a general motility defect.

**Intensity Dependence of Phototaxis to Green Light.** Fig. 3 shows the results for flies of various genotypes tested in the T maze for phototactic response to green light, as functions of I. Wild-type flies showed a threshold between log I = −6 and −5 (Fig. 3*A*). The response first increased with intensity, then diminished at the highest intensities tested. In contrast, flies homozygous for the *Ppb* mutation (*Ppb*/*Ppb* in Fig. 3*A*), were negatively phototactic over a range of green-light

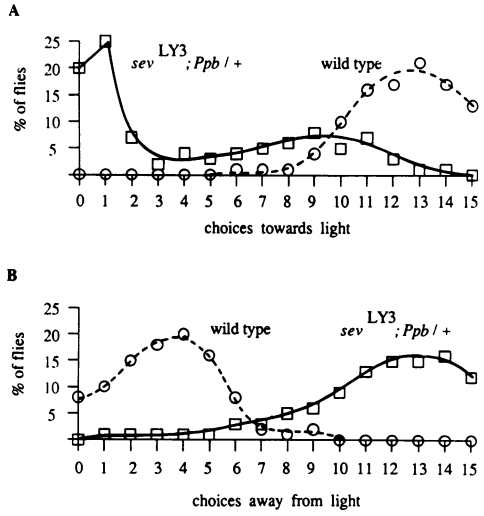


FIG. 2. Avoidance of white light by the double mutant $sev^{LY3}$; $Ppb/+$. Wild type (○) and $sev^{LY3}$; $Ppb/+$ (□) flies were tested in a countercurrent apparatus (21) in separate experiments for movement toward a fluorescent light source or away from it. (*A*) Phototaxis toward light. The flies began the experiment in tube zero at the end furthest from the light source. After 15 successive 30-sec trials, a record was made of the number of flies making each number of choices toward light over darkness. (*B*) Movement away from light. The flies began in tube zero at the end nearest the light, and a record was made of the number of choices toward darkness over light. Each curve represents the sum of 5–8 experiments totaling 200–400 flies (6–8 days old). Approximately 30% of the $sev^{LY3}$; $Ppb/+$ flies showed a broad distribution, which may reflect incomplete penetrance or low expressivity of the behavioral phenotype.

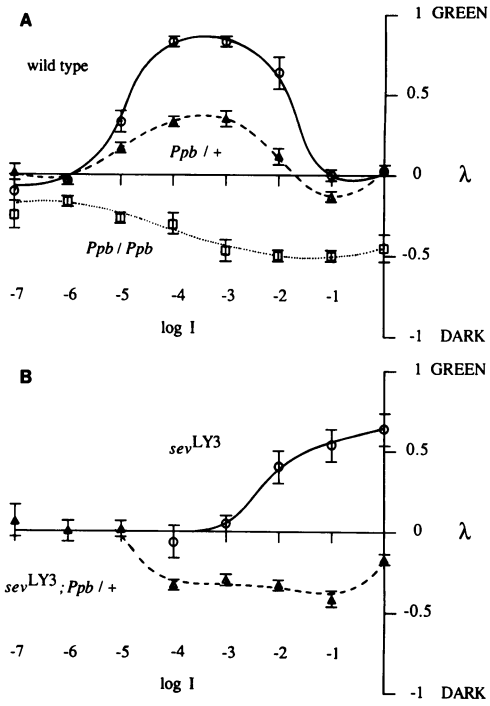


FIG. 3. Intensity dependence of phototaxis. The phototactic index λ was tested over a green-light intensity range of seven logarithms. (*A*) ○, wild type; △, $Ppb/+$; and □, $Ppb/Ppb$. At least 200 4- to 8-day-old wild-type, 450 4- to 6-day-old $Ppb/+$, or 200 4- to 8-day-old $Ppb/Ppb$ flies were tested for each data point. (*B*) ○, $sev^{LY3}$ and △, $sev^{LY3}$; $Ppb/+$. At least 150 4- to 6-day-old $sev^{LY3}$ flies or 250 4- to 6-day-old $sev^{LY3}$; $Ppb/+$ flies were tested for each data point. For wild-type flies, the ratio of intensities giving $\lambda = 0.5$ near threshold and in the high-intensity inhibitory range was the same as found by Heisenberg and Buchner (14) who measured a very different "slow" phototactic response.

intensity of six logarithms. Flies heterozygous for *Ppb* gave an intermediate profile ($Ppb/+$ in Fig. 3*A*). These phenotypes were characteristic of flies at any age from 1 to 10 days.

Flies carrying the $sev^{LY3}$ mutation were positively phototactic to green light at all intensities tested above threshold (Fig. 3*B*). The threshold of $sev^{LY3}$ flies increased with age. Flies aged 4–6 days had a threshold between log I = −3 and −2 (Fig. 3*B*), whereas 1- to 3-day-old flies had a threshold similar to the wild type (data not shown). Doubly mutant flies ($sev^{LY3}$; $Ppb/+$ Fig. 3*B*) were repelled by green light over an above-threshold intensity range of four logarithms. This negative phototaxis of $sev^{LY3}$; $Ppb/+$ flies is not fully manifest until 4–6 days of adult life; therefore, flies of at least that age were used in Fig. 3 for comparison.

Homozygous *Ppb* flies are repelled by UV light of 350 nm. The λ, measured in a T maze (UV vs. darkness; log $I_{UV}$ = 0), was −0.34 ± 0.05 for $Ppb/Ppb$, as contrasted with +1.0 for wild type. Thus, the defect of visual-information processing in flies homozygous for *Ppb* is not confined to green light. This condition cannot be tested in $sev^{LY3}$; $Ppb/+$ double mutants because $sev^{LY3}$ flies are much less sensitive to UV light (refs 11, 24; D.G.B., data not shown).

**Interaction of *Ppb* with *sev* Is Allele Specific.** To test whether the effect of *Ppb* in reversing phototaxis in combination with $sev^{LY3}$ could be due to its interaction with some mutation other than $sev^{LY3}$, flies were constructed in which all autosomes and the entire X chromosome outside of a three-map-unit region surrounding $sev^{LY3}$, had been replaced with the chromosomes of an isogenic C-S strain. This stock was established in our laboratory by R. Hackett using an isogenic strain provided by J. O'Tousa (University of Notre Dame). When introduced into this strain (designated $sev^{LY3\text{-}iA}$), the double-mutant combination $sev^{LY3\text{-}iA}$; $Ppb/+$ retained its negative phototaxis (Table 1). These data indicate that the interaction between $sev^{LY3}$ and *Ppb* is due to the $sev^{LY3}$ mutation itself or a second mutation very closely linked to it.

Further confirmation that *Ppb* interacts directly with *sev* comes from studies on eight different mutant alleles of *sev*. Females homozygous for each *sev* allele were mated to $sev^{LY3}$; $Ppb$/SM6a males. From each cross, some of the resulting male progeny had the *sev* allele in question on their X chromosomes and were heterozygous for the autosomal *Ppb* mutation. These flies were tested for phototaxis at a single intensity of green light. Only two of the eight alleles tested ($sev^{LY3}$ and $sev^{P3}$) were negatively phototactic in the presence of *Ppb* (Fig. 4). Thus, the interaction of *Ppb* with *sev* that causes negative phototaxis is allele specific. Combining each of the other six alleles of *sev* and *Ppb* caused a positive phototactic response at the particular intensity of green light used (log I = −1.5), as compared with *Ppb* in the absence of any *sev* mutation (Fig. 4; Table 1). These data also suggest an interaction between *sev* and *Ppb* in determining phototaxis.

Table 1. Reversal of phototaxis by the Photophobe mutation

| Genotype | Green/dark choice, λ ± SEM | *n* |
|---|---|---|
| Wild type | +0.51 ± 0.09 | 367 |
| $Ppb/+$ | −0.12 ± 0.03 | 580 |
| $Ppb/Ppb$ | −0.65 ± 0.06 | 248 |
| $sev^{LY3}$ | +0.40 ± 0.11 | 156 |
| $sev^{LY3}$; $Ppb/+$ | −0.41 ± 0.03 | 884 |
| $sev^{LY3}$; $Ppb/Ppb$ | −0.43 ± 0.05 | 275 |
| $sev^{LY3\text{-}iA}$; $Ppb/+$ | −0.32 ± 0.06 | 330 |

Flies were tested in a T maze for preference between darkness and green light of 550 nm (log I = −1.5). The reported λ is the mean of at least three independent measurements ± SEM. *n*, number of flies tested. A positive λ indicates phototaxis toward green light; a negative λ indicates a photophobic response.

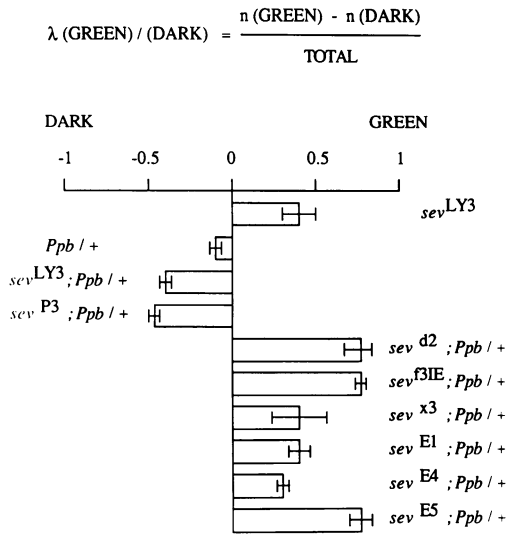


FIG. 4. *Ppb* interacts differently with different alleles of *sev*. Phototactic tests between darkness and green light (log I = −1.5). The phototactic index λ is reported for males heterozygous for *Ppb* and hemizygous for each of eight mutant alleles of *sev*. At least 250 flies of each combination were tested.

## DISCUSSION

This paper describes the isolation and characterization of a mutation on the second chromosome, Photophobe, that is a dominant suppressor of the abnormal color preference of the sevenless mutant and does not restore R7 to the adult eye. Flies of the genotype *Ppb/Ppb* or $sev^{LY3}$; *Ppb/+* are repelled from, rather than attracted toward, green light. Thus, the presence of a single gene mutation reverses the sign of phototaxis.

The normal neural circuitry would appear to include a mechanism for avoiding light. *Drosophila* larvae are negatively phototactic (25). Also, at high intensities of visible light, normal *Drosophila* adults show an inhibition of phototaxis. This inhibition is absent in *sev* flies, which remain positively phototactic at high light intensity. This is evident by comparing $sev^{LY3}$ (Fig. 3*B*) and wild type (Fig. 3*A*). This observation has been interpreted (14, 15, 24) as an indication that, at high light intensities, R7 and/or photoreceptor cell 8 inhibit the inputs of photoreceptor cells 1–6 into the phototactic response pathway. This inhibition would be relieved in *sev* mutants because R7 is missing. An alternative explanation is that the *sev* gene has another function besides its role in the development of R7, somewhere in the neuronal pathway that leads to the inhibition of phototaxis at high light intensity. The fact that the interaction between *sev* and *Ppb* is allele-specific, even though cell R7 is absent in all such double mutants, is further indication for the putative role of the *sev* gene. Because there is a mechanism in wild-type adult flies for inhibiting phototaxis, it is conceivable that this mechanism becomes constitutive at all light intensities in flies homozygous for *Ppb* or in flies doubly mutant for $sev^{LY3}$ and *Ppb*.

The specific interaction between *Ppb* and different *sev* alleles indicates that the products of these two genes are both involved in processing of visual information or in determination of cells involved in such processing. Such an epistatic interaction can occur if the gene products interact directly or if they function in a common pathway. An allele-specific interaction between two other mutations affecting the *Drosophila* visual system, *norpA* and *rdgB*, has suggested that both genes are involved in the phototransduction process (26). Such allele-specific interactions have been studied extensively in bacteria and yeast. For example, second-site mutations that suppress missense mutants of the bacteriophage P22 are almost always found in genes whose products interact physically with products of the suppressed gene (27).

The epistatic interaction between *sev* and *Ppb* is intriguing because it reveals a previously unknown complexity in the *sev* phenotype. All 20 existing *sev* mutant alleles have been isolated as male viable and fertile alleles, selected by one of two means. The first method was on the basis of their effects on phototaxis or color choice [e.g., $sev^{LY3}$ was originally isolated as a mutant with defective phototaxis (11); $sev^{d2}$ was isolated as a mutant with altered preference between green and UV light (16)]. The second method was by structural criteria indicating the absence of R7 (17). All these alleles lack R7, but some of them differ in their interactions with *Ppb*. These differences indicate that *sev* functions in cells other than R7 and subserves a function in phototaxis that is separable from its function in the determination of R7.

It is interesting that, in wild-type flies, the *sev* gene produces the same size transcript not only in developing eye discs, where the differentiation of R7 occurs, but also in the adult head (17, 28). This is true also for heads of mutant flies that completely lack eyes (P. Renfranz and S.B., unpublished work), and *in situ* hybridization indicates expression in the brain (J. A. Pollock and S.B., unpublished work). Flies carrying $sev^{LY3}$ have normal-sized *sev* transcript and protein detectable by an antibody that recognizes a C-terminal portion of the protein (29). Flies carrying $sev^{P3}$ make a shorter transcript due to deletion of 3′ genomic sequences (17). It is not known whether $sev^{P3}$ makes a partial *sev*-encoded peptide because the antibody-reactive segment is deleted. What distinguishes $sev^{LY3}$ and $sev^{P3}$, which interact with *Ppb* to enhance negative phototaxis, and the other six alleles of *sev* that increase positive phototaxis remains unanswered. (Fig. 4). Of the latter alleles, five show no detectable *sev*-encoded protein, whereas one does show such a protein. (U. Banerjee and S.B., unpublished).

From sequence similarity, Hafen *et al.* (28) have suggested that the *sev*-encoded protein may be an integral membrane protein with tyrosine kinase activity and an extracellular receptor domain. The normal *Ppb*-encoded product could conceivably act as a ligand for such a receptor in cells other than R7. This interaction could be important for the proper function, wiring, or differentiation of cells involved in the visual-information processing pathway. The isolation of *Ppb* is one step toward the identification of genes that affect the processing of visual information that guides phototaxis. This prompts an investigation of the visual system of these mutants for alterations in anatomy and physiology. Such studies have, indeed, revealed alterations in both structure and function of the first optic ganglion, the lamina, which will be described separately.

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