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DEVELOPMENT IN MOLECULAR GENETICS AND ELECTROPHYSIOLOGY IN INHERITED RETINAL DISORDERS

Review based on 20 years of research at the department of Ophthalmology in Lund

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Abstract

Retinits pigmentosa is said to be the most frequent reason for severe visual handicap among young people in Scandinavia today. The developments in the fields of electrophysiology and molecular genetics have increased our understanding of the pathophysiology of these disorders and have also improved our clinical competence, leading to a better understanding of the patients visual handicap and their prognosis. This is the first step forward towards our plan for the future, which is ultimately curing blindness caused by hereditary retinal degenerations.

Background

Hereditary retinal degeneration constitutes a heterogeneous group of eye disorders. They differ from each other in many aspects such as the mode of inheritance, the rate of progression, appearance by ophtalmoscopy and the type of visual handicap they cause among affected patients. Retinitis pigmentosa (RP) is known to be the most frequent cause of severe visual handicap among young people in Scandinavia today.

As we have no therapy for stopping the progression of these disorders, research in this field has been essential since several years. In this review I have summarized two research areas, which have been of major importance for improved evaluation of the different forms of retinal degeneration.

The development in electrophysiology has enhanced our possibilities to investigate and to identify retinal dysfunction, which also facilitates the understanding of the previously unknown pathophysiology in these disorders. Since Gösta Karpe in 1951 demonstrated the clinical value of electroretinography (ERG), it has been the method of choice for objective evaluation of cone and rod disorders (Björk & Karpe 1951). Further development in electrophysiology has made it possible to verify residual retinal function even if it constitutes less than 1% of the normal response. Recent development of the multifocal electroretinogram (mfERG), gives us the opportunity to identify local residual responses in selected areas of the macula.

Since Thaddeus Dryja in 1990 identified the first disease causing gene in families with dominant RP (ref) and introduced the candidate gene approach in ophthalmic genetics, the knowledge in this area has accumulated rapidly (Dryja et al. 1990). In Scandinavia the first family was identified by Thaddeus Dryja and his group, and the phenotype in this family with a mutation in the rhodopsin gene (ala-135-leu) was further described in 1992 (Andéasson et al. 1992).

During the same period the Swedish registry of patients with RP was introduced, which was a major step forward for the research in this area, and includes today approximately 2500 RP-patients, the majority of them from Sweden.

The development in electrophysiology and molecular genetics in combination with the introduction of the Swedish RP-registry has created a base for clinical research in this field.

Electrophysiology

The improvements in the technique of electrophysiology have come rapidly during recent years although the method has a long history. The Swedish ophthalmologist, Frithiof Holmgren, reported the first ERG in frog in 1865, and summarized that the ERG was a recording of action potentials produced within the retina upon stimulation with light (Holmgren 1865). In 1945, Gösta Karpe reported the ERG results from a study of 64 normal and 87 abnormal eyes, providing the initial basis for clinical investigations of retinal degenerations (Karpe 1945).

Because of the large variability in retinal dysfunction in different type of retinal disorders, further development of the ERG technic, was needed for analyzing all of these type of alteration in the retinal layers. In patient with retinits pigmentosa, the retinal function mostly is reduced with more than 90%, and for evaluate this group of patient in a proper way, a method for measuring residual small responses would be of main concern.

According to previous studies the human retina consists of a considerable amount of cones and rods, many more than we need for normal daily activities (Berson et al .1985). Thus, a person having only 5 % of normal retinal function, may actually have enough sight for a relatively normal life. From this point of view, a modified ERG method for detecting small residual responses, is of considerable clinical value. This is possible by using a sampling technique and an analogue filter during ERG-recordings (Andréasson et al. 1988). Digital filtering has further developed this technique which is currently used worldwide for identifying and monitoring patients with retinal degenerations. Residual retinal function less than 0,5% can now routinely be evaluated in clinical centres investigating inherited retinal diseases. During recent years this objective test of the retinal function has been of major importance, since clinical treatment trials now have become a reality for some of these disorders. (Fig.1)

Another topic has been the possibility to examine children and patients with multiple handicaps, who both need general anaesthesia for assessment of an ERG. In this group of patients there is a considerable need of objective evaluation of the visual handicap. Adequate ERG examination of these patients during general anaesthesia is possible today, taking in account the effects of anaesthetics on photoreceptor function, during such a procedure (Andréasson et al 1993). Knowledge of the development of cone and rod function during the first year of life, in combination with an adequate method for ERG during general anaesthesia, has enhanced our possibilities in identifying different form of retinal dysfunction in this group of patients (Andréasson et al 1996). (Fig. 2)

The classical (full-field) ERG is a reliable method for measuring responses from rods and cones throughout the entire retina. However, it is also important to obtain responses from localized areas of the retina, especially the macula region. A few years ago the most widespread method used was the Doran Focal ERG, which can be characterized as a rebuilded ophthalmoscope, developed for obtaining the cone ERG from the macular region (Sandberg et al. 1979).

During recent years the mfERG has been developed and introduced by Erich Sutter, which is a more adequate method for identifying dysfunction in localized area in the central part of retina and in the macular region (Sutter & Tran 1992). By dividing the stimuli into 60-240 different areas and by illuminating the fundus with infrared-light during stimulation, it is possible to objectively identify, recognize and monitor retinal dysfunction of localized areas in the macular region (fig. 3). Investigation and interpretation of these responses has enhanced our possibility to better understand the retinal function in different disorders, which not always is consistent with the retinal and macular appearance especially in children and young patients.

By introducing the mfERG, it became possible also to measure responses from the visual cortex. The standard visual evoked potential (VEP) has been a routine clinical method, but since it is a response to stimulation of the entire retina, the standard VEP does not give any topographical information of the retinal function or the function of the visual pathway (Bengtsson et al. 2005). This limitation could be overcome by using multifocal stimulation. Using this technique, many small areas of the retina are stimulated and separate responses from the from different parts of the visual field can be obtained (Baseler et al 1994; Baseler

& Sutter 1997). The multifocal VEP (mfVEP), which assesses the cortical responses from localized areas in the retina, has been of major value for understanding and detecting disturbances in the visual pathways. This method gives us the possibility to separate retinal function from visual pathway dysfunction (Gränse et al. 2004). (Fig. 4)

The international standard from the ISCEV is of major important for standardizing the electrophysiologic examinations (Marmor et al 2004). Because of continuously developing new methods and the needs for more specific examination of patients with different types of retinal degeneration, further development of specific techniques are most important, in addition to the recommendations from ISCEV.

Molecular genetics

The progress in the field of molecular genetics has extended our knowledge concerning different proteins in the retina, which are involved in different retinal disorders. The following description of some specific genes causing different types of retinal degeneration, demonstrates the value of this research. (Table 1)

Rhodopsin

In 1992 we described the first Scandinavian family with retinitis pigmentosa and a mutation in the rhodopsin gene (Andréasson et al. 1992). The genotype with a mutation arg-135-leu altered the function of the rhodopsin protein leading to an autosomal dominant form of retinitis pigmentosa. Compared to other families with dominant form of RP and a mutation in this gene, this family seemed to have a more severe form of RP verified by ophthalmologic examination and full-field ERG (Ponjavic et al.1997). All members of this family had early onset of night blindness and a considerable field loss already as teenagers. Full-field ERG demonstrated no rod function and a markedly reduced cone function early in life. Fifteen years ago this family seemed small, but the pedigree has grown and it now involves a large family in the middle part of Sweden. (fig 5)

Today we have knowledge of approximately 70 different mutations in this rhodopsin gene, which alters the function of the protein in different ways. In order to understand the different modifications of the rhodopsin function it has been divided into different groups. Class I can be described as a mutant causing an abnormal transport to the plasma membrane and class II as a mutant defective in folding and having the lack of regenerability. This classification is important not only for understanding the pathogenesis of hereditary retinal degenerations but also for clarifying the clinical phenotype. According to several studies mutations in the region 347 (Class 1) demonstrate a more severe form of RP. In addition to this findings treatment trials in transgenic mouse have demonstrated that phenotype according to class II, seems to be a better responder to vitamin A treatment (Li et al.1998).

Recently a class III mutation type has been added, which in fact includes the mutation previously described in our Scandinavian family (Chuang et al. 2004). Mutations in codon 135 rhodopsin alter the photoreceptor function by creating a complex of rhodopsin-arrestin, which separates this class from the rhodopsin mutation classes I and II. The classification also explains why the phenotype in our previously described family frequently causes a more severe form of RP.

Best vitelliform macular dystrophy, VMD2 Bestrophin

Several genes involved in photoreceptor function have been identified, and different mutations in these genes cause different types of RP. Besides proteins causing photoreceptor dysfunction, there are other proteins, involved in the function of the pigment epithelium, that can cause different types of RP. One such protein is bestrophin responsible for autosomal dominant vitelliform dystrophy of macula, which is a common disorder recognized, at least in the Swedish community, since the 1800th century.

Best macular dystrophy is known in Scandinavia through the initial studies of Yngve Barkman, a Swedish ophthalmologist, who described a large family with an unusual form of macular degeneration correlated to one gene source in the 17th century.(Nordstrom & Barkman 1977). The disease causing gene was identified by Konstantin Petrukhin (Petrukhin et al. 1998) and since then several mutations in this gene have been identified . The altered protein has been further examined. The different phenotypes relating to different mutations have been described in several families (Ponjavic et al. 1999; Eksandh et al. 2001)

The protein is localized in the pigment epithelium cell membrane and is responsible for the transportation over the membrane. Dysfunction of the bestrophin protein inhibit the transportation over the membrane and affects the electrical resistance, which may be the basis for the loss of the electrical peak during the light adaptation phase of the EOG (Marmorstein et al 2000; Sun, et al. 2002) . On the other hand, the full-field ERG demonstrates normal responses from the photoreceptors. The mfERG, however, often reveals reduced responses in the macular region. This may reflect that at least in the retinal periphery the photoreceptor function is unchanged even if the alteration in the electricity in the pigment epithelium is changed.

A normal full-field ERG and a pathological EOG has since several years been the cornerstone for diagnosing this disorder and typical for its clinical phenotype. More and more families are being tested for mutations in the bestrophin gene, thereby increasing our knowledge of this disease. Recently new clinical phenotypes have been identified, demonstrating that there may exist additive factors influencing the bestrophin function. Patients with certain mutations in the bestrophin gene have been found to have a normal EOG and less visual symptoms, but also the opposite has been described, some patients having a more generalized and widespread retinal degeneration. Because of these findings several studies have been conducted regarding bestrophin mutation in AMD, but no association to AMD has been confirmed (Kramer et al 2000). Combined electrophysiology with mfERG and OCT has been of value for characterizing the phenotypes associated with mutations in the bestrophin gene.

RPGRP, RP2-protein and RPGRIP

X-linked RP, which appears to be the most progressive form of retinal degeneration, is associated with a severe visual handicap early in life. At least six genes causing this disorder have been identified (Breuer et al. 2001). One of the more essentials proteins, at least in the Swedish community, is the retinitis pigmentosa GTPase regulator protein RPGR. Mutation in this gene *RPGR-orf15*, seems to be the most common cause of X-linked RP. The *RPGRP* gene is expressed throughout the outer segments of human rod and cone photoreceptors and the protein seems to be of major importance for the viability of the receptors (Khanna et al. 2005). (Fig 6)

Because the severity of this disorder, and because the carrier state often demonstrates a variable findings, X-linked RP has been of special interest for research. As several phenotypes have been described (also in Scandinavia) associated with different mutations in the *RPGR-orf 15* gene, we today have considerable knowledge concerning this disorder (Andréasson et al 1997; Andréasson et al 2003). The new technique with full-field ERG and bandpass filters has made it possible to evaluate residual retinal function in these RP patients and follow the rate of progression in an objective manner.

Another protein important in X-linked RP is the RP2 protein. This protein is localized to the plasma membrane in both rod and cone photoreceptors, and if the gene is mutated the defect protein can cause retinal degeneration involving both cones and rods. The phenotype is variable, depending on the disease causing gene, but several reports during recent years seem to agree that mutation in the *RPGRP* gene is a more severe form of retinitis pigmentosa compared to the RP2 disorder (Ponjavic et al. 1998;Sharon et al 2003).

The carrier state of X-linked RP has since several years been of major interest because of the variability of the phenotype in different carriers. It is important to identify carriers in families with X-linked RP, in order to give genetic counceling. Full-field ERG in combination with a clinical eye examination is of value because, according to several reports, in this way the carrier state can be detected in approximatley 80 % of examined carriers. Investigation of the responses from the 30 Hz flickering light stimulation often demonstrate a delayed cone b-wave implicit time in female carriers. These findings are a major step forward in the field of X-linked RP (Andreasson & Ehinger et al. 1990).

As the responses from mfERGs reflect the function of small, localised areas in the retina, the method has been of interest in identifying carriers of X-linked RP, and in further evaluating retinal function in these patients. It has been described that carriers of X-linked RP can have patchy areas of dysfunction in the retina, which is logical considering our knowledge of mosaicism. These findings have now been verified in a few reports and are of major importance for further insight in X-linked RP (Andersson-Gronlund et al 2003; Vajaranant et al 2002).

In this context concerning mutations in the *RPGR gene*, it is worth mentioning that another protein, RPGRIP1, interacts with the retinitis pigmentosa GTPase regulator protein (RPGR) in the photoreceptor outer segment. Mutations in this gene *(RPGRIP1)* can, in recessive forms, be responsible for a severe form of RP known as Lebers retinal degeneration. Mutations in this gene have been identified also among patients from the Swedish community (McGee et al. 2001).

Retinitis pigmentosa in association to other disorders

Since several years our knowledge of atypical types of RP has grown and today both the genotype and the phenotype is known in several of these complex forms of retinal degeneration. As some of these disorders are associated with other types of handicap an early diagnosis is important, for better awareness of the visual handicap and for better understanding of the patients visual complaints. During recent years the genotype and the phenotype has been identified in disorders such as Spielmeyer-Vogt, Lawrence Moon Bardet Biedl (LMBB), Usher's syndrome and the CDG I syndrome, which will be focused on in this paper.

Congenital disorder of glycosylation CDG I syndrome (PMM2 phosphomannomutase-2)

This multi organ disorder was initially described in 1987 as a neurological syndrome associated with signs of demyelinization and multiple serum glycoprotein abnormalities. During childhood these children have a marked developmental delay, muscular weakness, ataxia, slowly progressive poly neuropathy and secondary skeletal deformation (Jaeken et al. 1987).

Initially the ocular symptoms were defined as esotropia and visual disturbance (Strömland et al 1990). Later the full-field ERG could verify the night vision problems demonstrating a non recordable rod response. The ERG examinations revealed that all of these patients had nyctalopia.

One major concern was that the fundus appearance in young patients did not demonstrate any changes that are usually found in retinal degenerations.(Fig 7) This made it complicated to identify their visual handicap at young age. However, examination with full-field ERG in early age could detect the retinal degeneration (Andréasson et al 1991). Besides the reduction of the cone and rod responses, the cone b-wave implicit time (IT), tested by 30 Hz flickering white light, was delayed. It is known that a prolonged IT is a predictor of progressive retinal degeneration (Berson 1993). These observations could demonstrate that patients with the carbohydrate-deficient glycoprotein syndrome, besides their neurological symptoms, also had a progressive retinal degeneration, with defined alterations in the ERG affecting their visual outcome. Further evaluation has demonstrated that, compared to most other classical forms of RP, the rate of progression is slower, and that the progress is variable in different patients with CDG.

The glycoprotein abnormalities in these patients have also been compared to other, more classical forms of RP, by testing carbohydrate-deficient transferrin (CDT) in serum. No similar glycoprotein abnormalities could be identified in a large group of tested RP-patients (Andréasson et al 1992).

Conclusion

The developments in the fields of electrophysiology and molecular genetics have increased our understanding of pathophysiology in patients with hereditary retinal degeneration, and have also improved our clinical competence in classifying the different types of diseses, leading to a better understanding of the patients visual handicap and their prognosis.

This is the first step forward towards our plan for the future, which is ultimately curing blindness caused by hereditary retinal degenerations.

Table 1

Summary of identified causatives proteins for different retinal disorder examined at the Department of Ophthalmology, Lund in collaboration with other laboratories.

BCM (Red and green pigment) [1]
Bestrophin[2]
CHM (Rab escort protein) [3]
CLN3 (CEROID LIPOFUSCINOSIS, NEURONAL 3 protein) [4]
CNGA3 (a-subunit of the cone photoreceptor cGMPgated channel) [5]
CNGB3 (b-subunits of the cyclic nucleotidegated cation channel (CNG) in cone photoreceptors) [5]
DDP (deaf-ness/dystonia peptide protein) [6]
Digenic A135T rodopsin; A16H ROM1 (rod outer segment protein 1) [7]
RETGC-1 GUCY2D (guanylate cyclase 2D) [8]
IMPDH1 (inosine monophosphate dehydrogenase 1) [9]
NYX (nyctalopin) [10]
OPA1 -protein[11]
Peripherin/RDS (Retinal degeneration slow protein) [12]
PMM2 (PHOSPHOMANNOMUTASE 2) [13]
Rhodopsin[14]
RLBP1 (cellular retinaldehyde-binding protein) [15]
RP2 protein[16]
RPGR ORF15 protein [17]
RPGRIP (RPGR-interacting protein)[18]
XLRS1 (RS-protein) [19]

[1]Andréasson 1991, [2]Petrukhin 1998; Ponjavic V 1999; Eksandh et al 2001, [3]v Bokhoven 1994; Ponjavic 1995, [4]Eksandh 2000, [5]Pusch 2000; Wissinger, 2001;Eksandh 2002; Kohl et al 2005, [6]Tranebjærg 1995; Ponjavic 1996, [7]Jacobson 1998, [8]vGhelue 2000, [9]Schatz 2005, [10]Pusch, 2000; Jacobi 2002, [11]Thiselton 2002, Gränse 2003, [12]Ekström 1998a; Ekström 1998b; Ekström 1998c, [13]Andréasson 1991, [14]Andréasson 1992; Ponjavic 1997a; Ponjavic 1997b, [15]Gränse 2001, [16]Ponjavic 1998, [17]Fujita 1997; Andréasson 1997; Buraczynska 1997; Bauer 1998, [18]McGee 2001, 19Eksandh 2000; Hiriyanna 1999; Eksandh 2005

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Figure 1

Full-field 30-Hz electroretinograms from a normal subject and four patients with retinitis pigmentosa tested at an 11- to 15-year interval. Stimulus onset, vertical markers; calibration symbol (left column, lower right) designated 100 µV vertically for the normal subject and top three patients and 40µV vertically for the bottom patient and 50 msec horizontally for all traces; calibration (right column, lower right) designated 2 µV vertically for the dominant , X-linked, and isolated patients and 20 msec horizontally for all traces. B-wave implicit times are designated with arrows. RP, retinitis pigmentosa.

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Figure 2

Full-field electroretinograms from four infants with different types of retinal degeneration and one normal infant. The three panels to the left show two superimposed single flash recordings from blue, red and white light. The two right panels show the responses to 30 Hz flickering light. (Normal ERG value (±2σ for children during general anesthesia with white flash

191±70µV, 30 Hz flickering white light cone b-wave amplitude 54,3±30µV and cone b-wave implicit time 30,4±2,8 ms).

(From Andréasson S, Ponjavic V: Full-field electroretinograms in infants with hereditary tapetoretinal degeneration. Acta Ophthalmol Scand 1996; 74 (Suppl): 219).

Figure 3

Mf ERG recording, demonstrating the visualization of retina with the infrared camera.

Figure 4

a. Standard VEP, which demonstrate no topographical information about different parts of the retinogeniculo-cortical pathways, or of the visual cortex.

b. MfVEP with topographical information from the optic pathway.

Figure 5

Recent pedigree of the initially Scandinavian family described 1992 with a rhodopsin mutation arg-135-leu.

Figure 6

Illustrating the RPGRIP and RPGR protein close to the connecting cilia in the rod.

Figure 7

Fundus picture of four patients with different degenerative disorders

A. Carrier of XLRP (*RPGR*–microdeletion exons 8–10)

B. XLRP splice mutation *(RPGR*–IVS7 + 5 G >A)

C: Vitelliform maculadegeneration (T357C *Bestrophin*)

D. CDG1 (*PMM1*)

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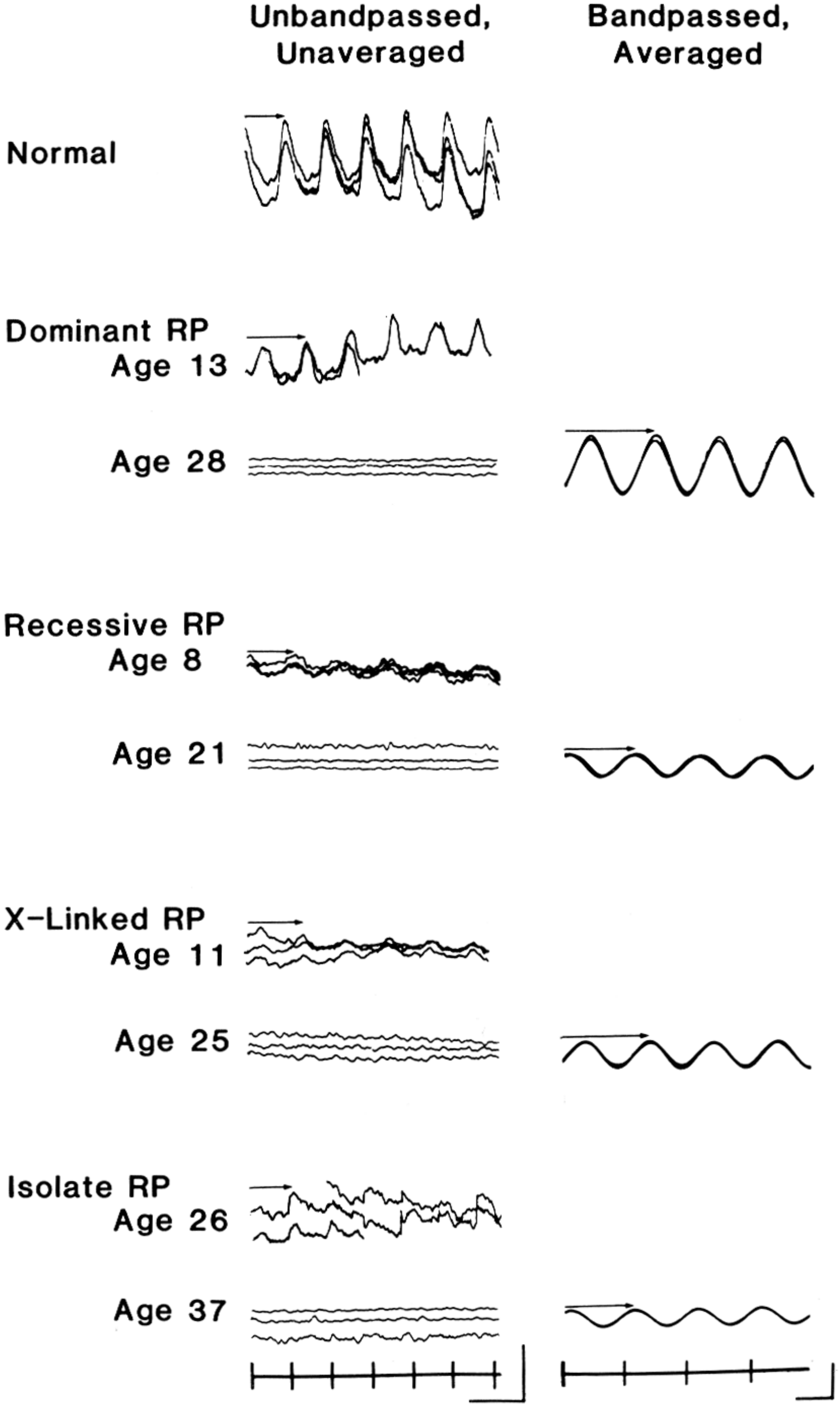
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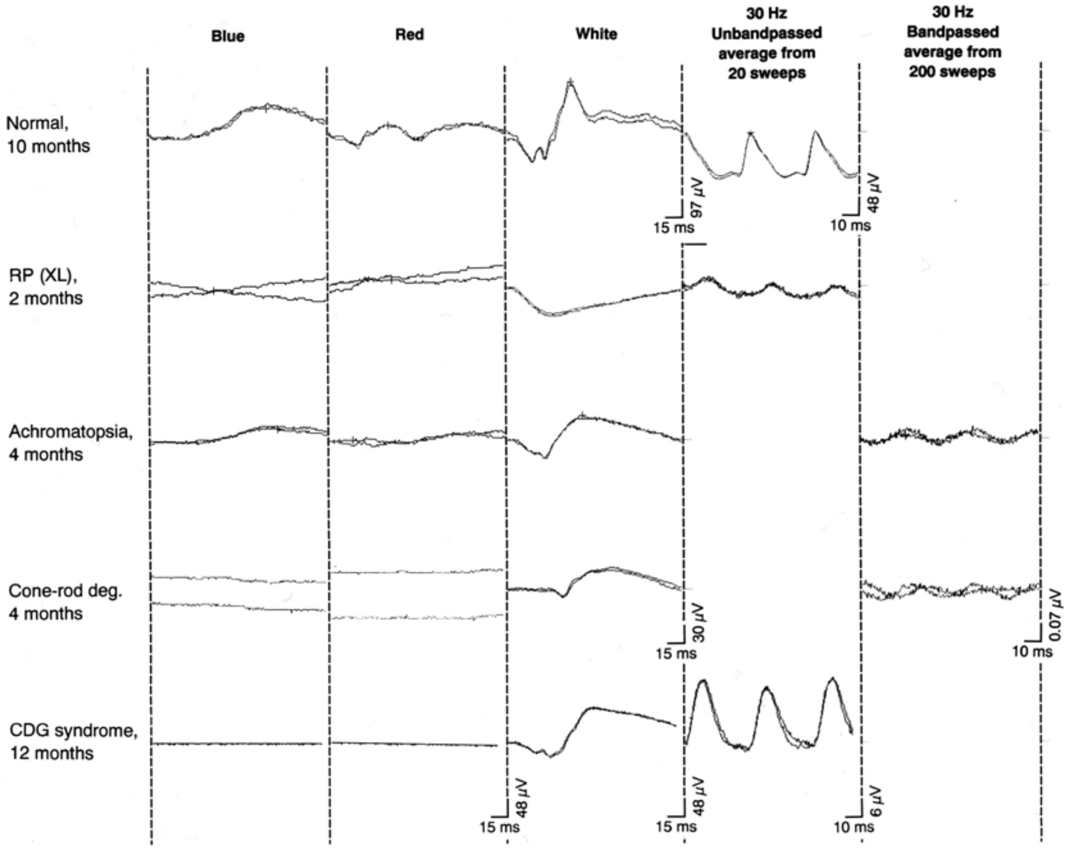
Age 26
Age 37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Achromatopsia, 4 months
Cone-rod deg. 4 months
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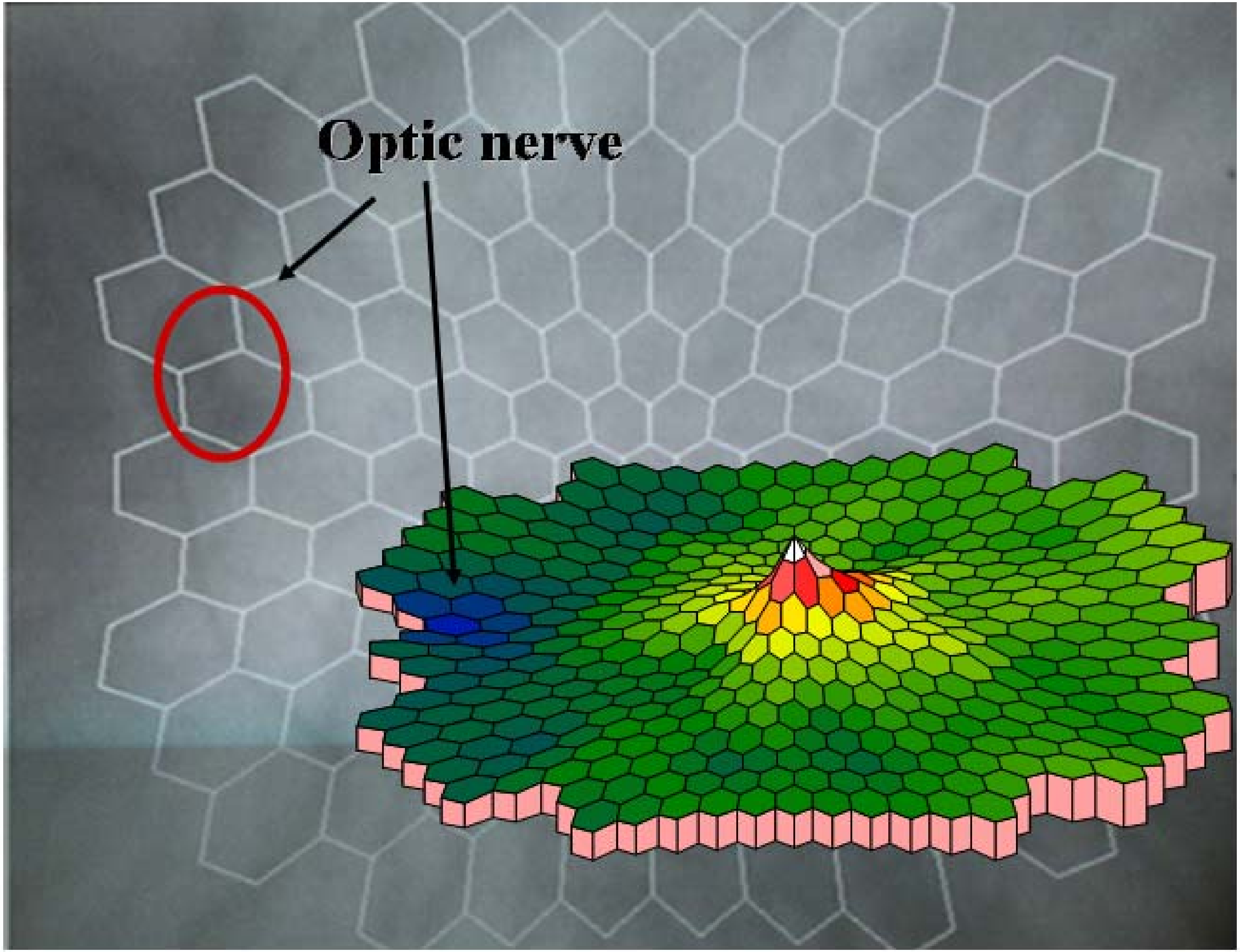
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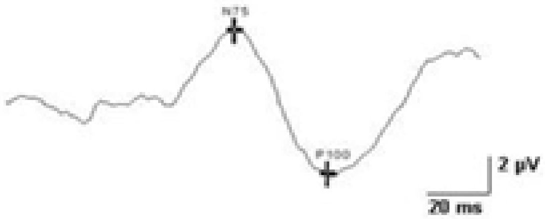

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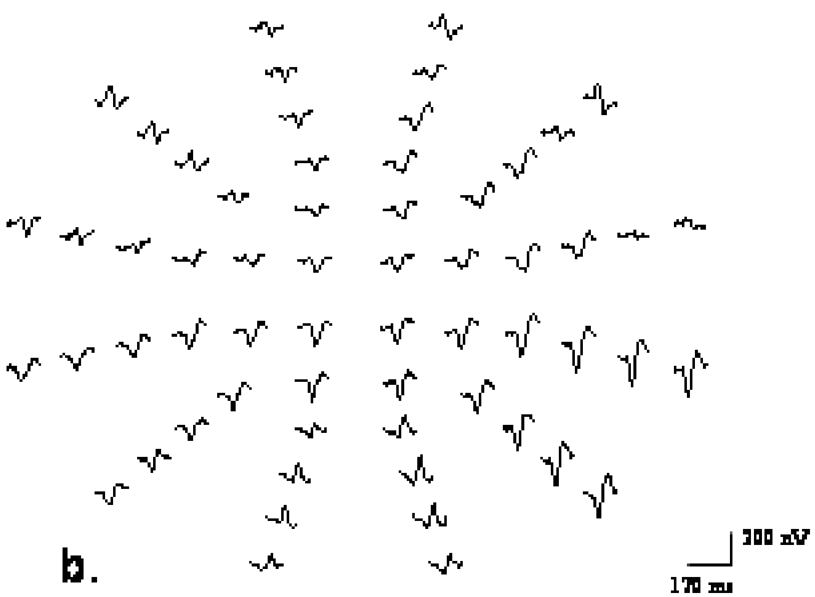

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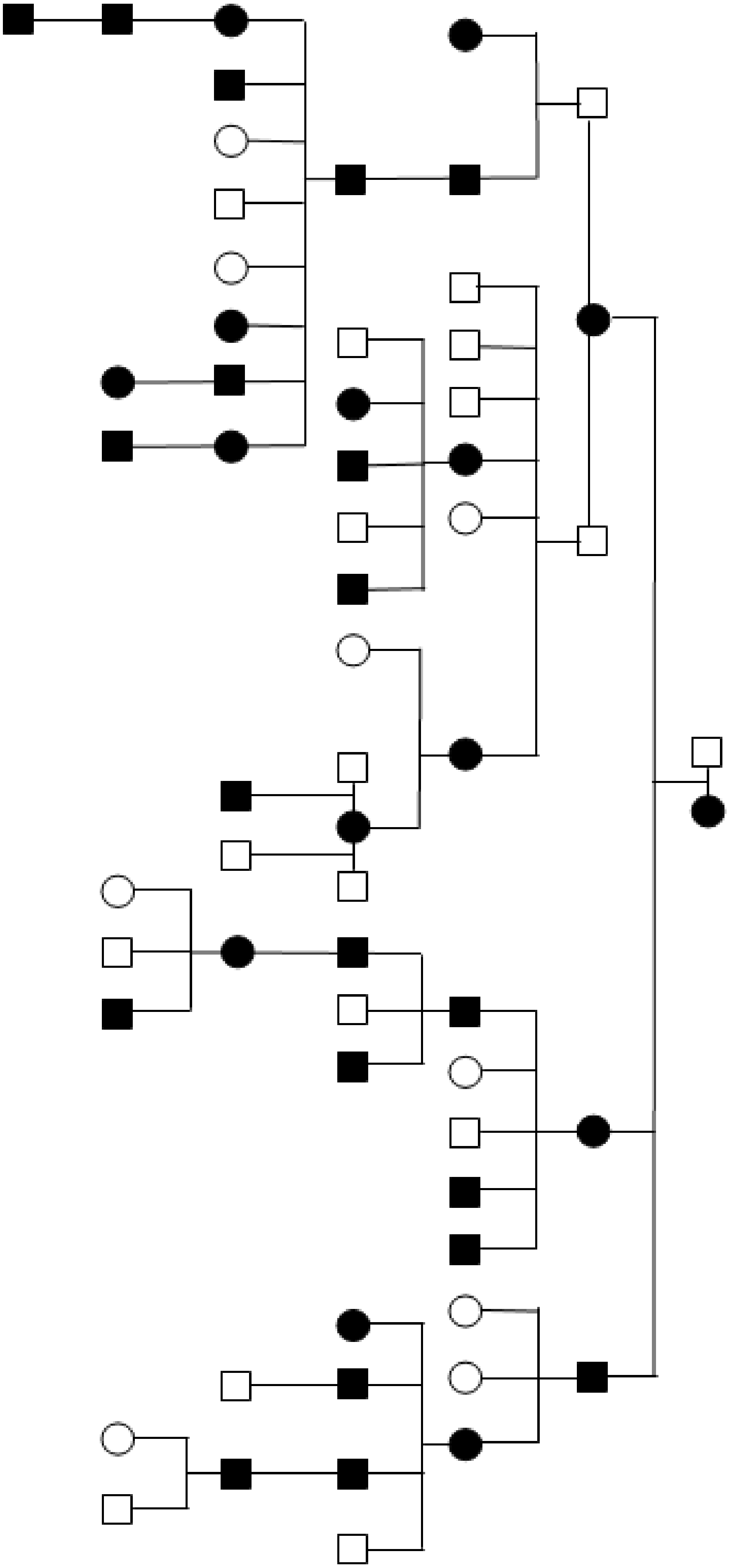

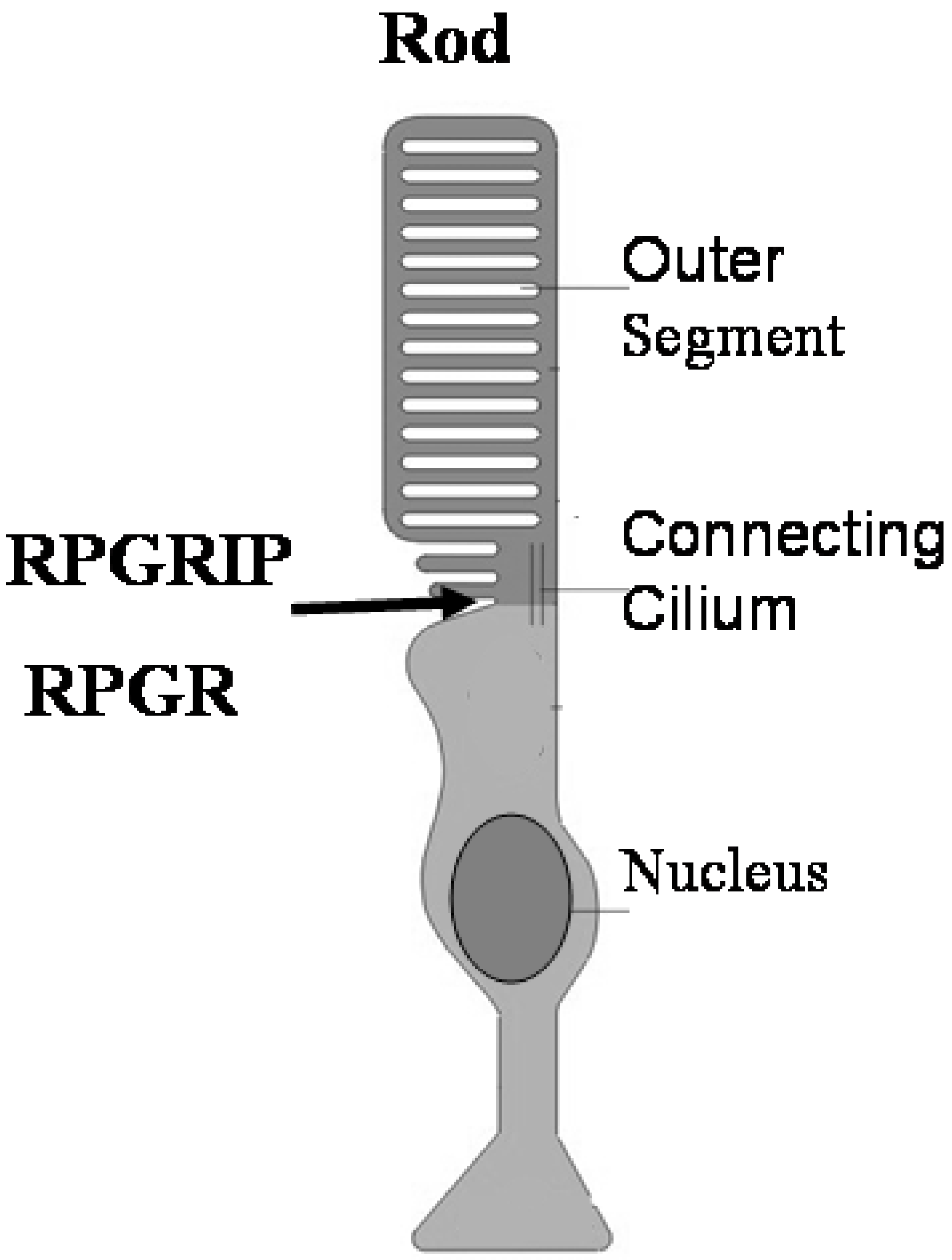

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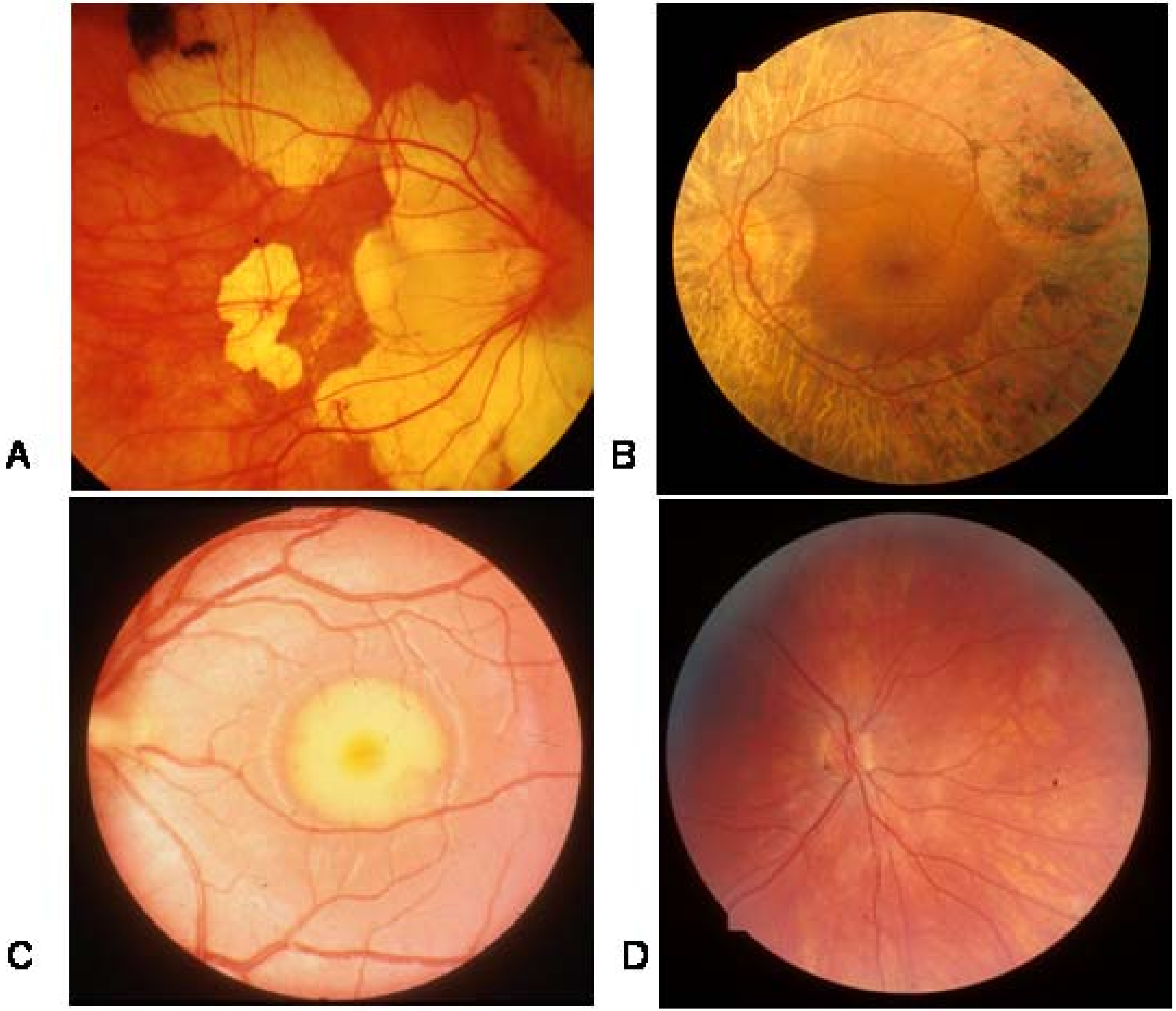
RPGR
Nucleus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