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Spotlight on vision

Gene discovery and prevalence in inherited retinal dystrophies

Découverte de gènes et prévalence dans les dystrophies rétiniennes héréditaires

Christian P. Hamel

Inserm U.1051, institut des neurosciences de Montpellier, hôpital Saint-Éloi, BP 74103, 80, rue Augustin-Fliche, 34091 Montpellier cedex 5, France

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ABSTRACT

Inherited retinal dystrophies are Mendelian neurodegenerative conditions classified as pigmentary retinopathies, macular dystrophies and others. Over a 21-year period, from 1990 to 2011, we have screened in Montpellier 107 genes in 609 families and have identified a causal mutation in 68.5% of them. Following a gene candidate approach, we established that *RPE65*, the isomerohydrolase of the visual cycle, is responsible for severe childhood blindness (Leber congenital amaurosis or early onset retinal dystrophy). In an ongoing study, we screened the genes in a series of 283 families with dominant retinitis pigmentosa and we have estimated that 80% of the families have a mutation in a known gene. A similar study is currently undergoing for autosomal recessive retinitis pigmentosa. Finally, we have identified *IMPG1* as a responsible gene for rare cases of macular vitelliform dystrophy with a dominant or recessive inheritance.

Mots clés :
Dystrophies rétiniennes héréditaires
Rétinite pigmentaire
Dystrophie maculaire
Criblage moléculaire
Amaurose congénitale de Leber
Dystrophie vitelliforme maculaire

RÉSUMÉ

Les dystrophies rétiniennes héréditaires sont des neurodégénérescences, maladies génétiques mendéliennes classées en rétinopathies pigmentaires, dystrophies maculaires et autres. Sur une période de 21 ans, de 1990 à 2011, nous avons criblé à Montpellier 107 gènes dans 609 familles et identifié une mutation causale dans 68,5 % d'entre elles. Suivant une approche de gène candidat, nous avons établi que *RPE65*, l'isomérohydrolase du cycle visuel, est responsable de cécités sévères de l'enfant (amaurose congénitale de Leber ou dystrophie rétinienne précoce). Dans une étude en cours, nous avons criblé les gènes responsables dans une cohorte de 283 familles, avec une rétinite pigmentaire dominante autosomique, et estimé que 80 % des familles ont une mutation dans un gène connu. Une étude similaire est en cours pour les rétinites pigmentaires récessives autosomiques. Enfin, nous avons identifié le gène *IMPG1* comme responsable de rares cas de dystrophie vitelliforme à hérédité dominante ou récessive.

Email address: christian.hamel@inserm.fr.

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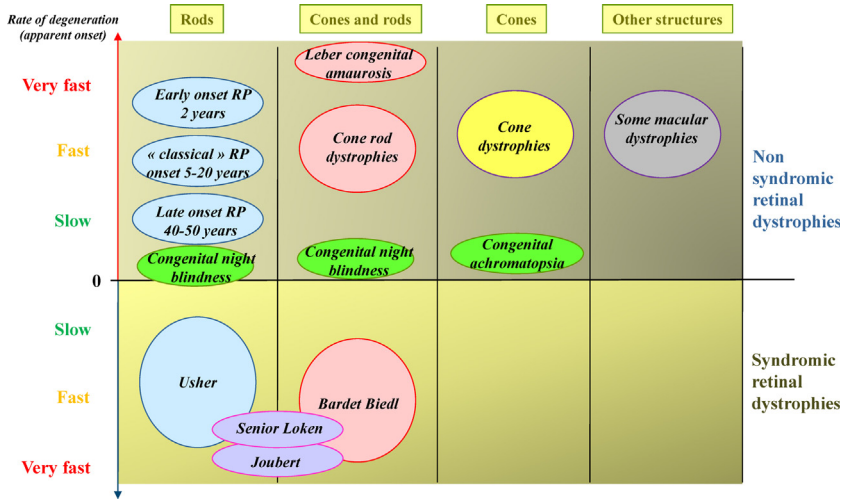

Fig. 1. (Color online) Classification of inherited retinal dystrophies in function of the type of involved photoreceptors, rate of degeneration and syndromic/non-syndromic conditions.

1. General presentation of inherited retinal dystrophies

Inherited retinal dystrophies (IRDs) belong to the vast group of neurodegenerations. They are Mendelian genetic conditions leading to the dysfunction and cell death of various retinal cell types, thus causing a progressive loss in vision. Cases where the functional defect is predominant are often considered as non-progressive congenital abnormalities, whereas those in which cell death predominates lead to irreversible vision loss (Fig. 1). In many of these diseases, there is progressive appearance of pigmentary deposits in the retina as a consequence of changes in the outermost layer of the retina called the retinal pigment epithelium (RPE), which is often secondary to the death of the retinal photoreceptors (PRs). Depending on the localization of the pigment deposits in the retina and of the accompanying retinal atrophy, one distinguishes the pigmentary retinopathies when the initial lesions are located in the peripheral regions of the retina, outside the central macula, and the macular dystrophies when the lesions are mainly located in the macula lutea. Thus, patients with pigmentary retinopathies typically undergo alterations in their peripheral visual field with moving difficulties, especially at low light levels, while they conserve until late in the course of the disease their reading capacities. In contrast, patients with macular dystrophies have early difficulties in reading and face recognition while they still move freely in their environment. When a severe degeneration is present at birth, usually both in retinal periphery and in the macula, the pigmentary retinopathy is called Leber congenital amaurosis. Pigmentary retinopathies are further subdivided in rod-cone dystrophies when the mutation has a direct pathogenic effect on the PRs rods, the cells which are sensitive to low light levels (night), and in cone-rod dystrophies when the PRs cones, which are sensitive to high light levels (daylight), are predominantly affected. Retinitis pigmentosa, the most frequent form of IRDs, corresponds to the rod-cone dystrophy. Less frequent are the cone dystrophies corresponding to a pathogenic effect only or mainly on cones.

In contrast with the blinding retinal degenerations described above, there are conditions due mainly to cell dysfunction in the retina. These are the congenital stationary night blindness in which the dysfunction takes place in the PRs rods or in the synapses of PRs with bipolar cells. In other conditions, the dysfunction occurs in cones leading to congenital achromatopsia and other forms of cone dysfunctions. Among IRDs, there are also vitreoretinopathies in which retinal glial cells and vessels are abnormal with as consequences retinal detachment, vitreous hemorrhages and PRs degeneration. When the choroid is affected, the conditions are named chorioretinopathies. There are subtypes of IRDs, relatively poorly defined, with difficulties in movement detection and adaptation to various light levels, which could be due to defects in specific subsets of retinal neurons like the amacrine cells. Finally, hereditary optic neuropathies, due to the degeneration of the retinal ganglion cells, are not classified among the IRDs because the major sign is the atrophy of the optic disc head visible in fundus whereas the retina has a normal aspect (Fig. 2).

2. Overview of the genes involved in IRDs

In almost all groups of IRDs, the causative genes are many. Today, there are more 200 genes causing IRDs (https://sph.uth.edu/Retnet/sym-dis.htm). These genes code for proteins involved at many different levels in the retina (Fig. 3), being classified in function of the metabolism and of the cell type involved. The most important gene category is the one coding for proteins of the connecting cilium (ciliary proteins) and of the calical process of PRs (microvilli present at the apical end of the PRs inner segment), representing roughly 25% of all *IRD* genes. Many of them cause both non-syndromic pigmentary retinopathies and syndromic forms like the Usher (retinitis pigmentosa associated to deafness), Bardet Biedl, Joubert and Senior Loken syndromes. The genes coding for proteins of the visual transduction are not as many but they are responsible for non-syndromic forms in