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SHORT COMMUNICATION

Phenotypic intrafamilial variability associated with S212G mutation in the RDS/peripherin gene

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PURPOSE. *To describe an Italian family in which two separate phenotypes (retinitis pigmentosa and adult onset vitelliform macular dystrophy) are associated with an identical mutation (S212G) in the peripherin/RDS gene. This mutation has already been reported in patients with retinitis pigmentosa, but it has never been previously detected in association with adult onset vitelliform macular dystrophy.*
METHODS. *A 38-year-old woman complained of bilateral mild metamorphopsias and on ophthalmologic examination she showed the clinical phenotype of adult onset vitelliform macular dystrophy. Her 62-year-old mother was clinically diagnosed with a retinitis pigmentosa, with a severe clinical course.*
RESULTS. *In both patients, molecular genetic analysis revealed a 874A→G transition in the exon 2 of the RDS gene leading to the amino acid change of S212G.*
CONCLUSIONS. *Peripherin/RDS S212G mutation may have damaging effects on the formation and stability of the photoreceptors' disk structure and may be associated with different clinical phenotypes, even in the same family. Intrafamilial phenotypic variability has been reported for other RDS mutations; this supports the possible influence of modifier genes or environmental factors in the clinical expression of RDS gene variants. Moreover, it suggests that in patients with retinal degeneration and peripherin/RDS mutation, caution should be taken both in using molecular genetic results to predict the clinical course of the disease and in offering genetic counseling. (Eur J Ophthalmol 2007; 17: 1000-3)*

KEY WORDS. *Adult onset vitelliform macular dystrophy, Peripherin/RDS gene, Retinitis pigmentosa, Intrafamilial variability*

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INTRODUCTION

The human retinal degeneration slow gene (peripherin/RDS), located on the short arm of human chromosome 6, encodes a membrane protein which contributes to the maintenance of the photoreceptors' structure. Peripherin/RDS protein consists of a sequence of 346 amino acids, and is composed of four putative membrane-spanning domains linked to each other by one intracytoplasmic and two intradiscal loops. The intradiscal D2 loop is thought to represent an important functional part of the protein which plays a relevant role in the development and stability of rod and cone disks. Mutations in the peripherin/RDS gene have been associated with a spectrum of retinal phenotypes including pattern dystrophies, autosomal dominant retinitis pigmentosa, cone-rod dystrophy, central areolar choroidal dystrophy, and retinitis punctata albescens (1). Moreover, RDS mutations have

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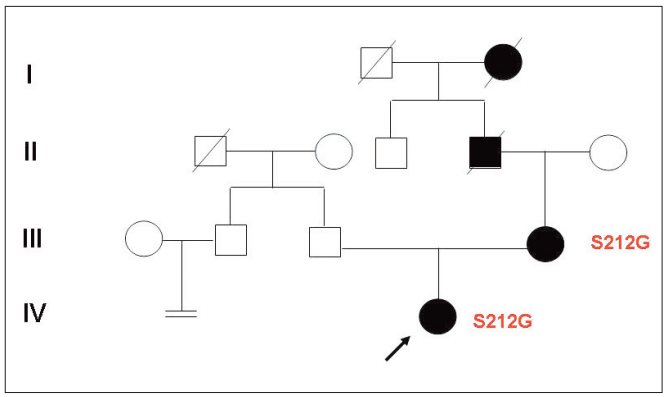

Fig. 1 - *Pedigree of family with RDS/peripherin S212G mutation and different phenotypes of retinal degeneration. Square: male; Circle: female; Solid symbol: affected; Open symbol: unaffected.*

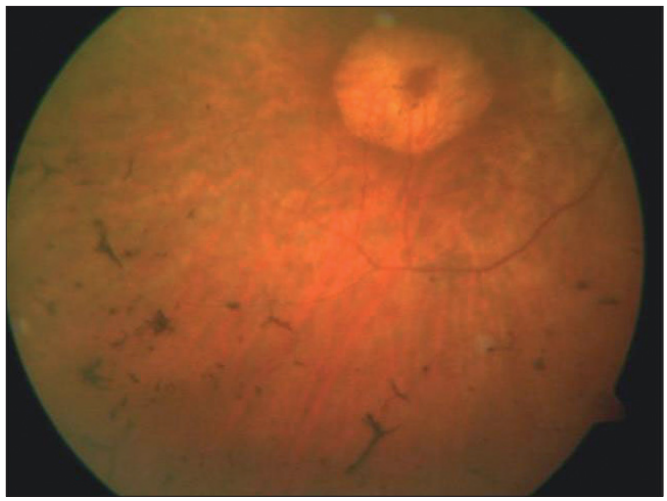

Fig. 2 - *Posterior pole of Patient III-4 showing midperipheral atrophy of the retinal pigment epithelium with bone-spicule pigment deposits and sharply demarcated macular atrophy.*

been associated with intrafamilial phenotypic variability - probably due to the influence of modifier genes and/or environmental factors (2, 3).

In this article, we report for the first time the detection of a specific peripherin/RDS mutation in a patient with adult onset vitelliform macular dystrophy - a peculiar pattern dystrophy. Another member of the same family, carrying an identical mutation, showed the clinical phenotype of retinitis pigmentosa (Fig. 1).

Case report

The patient (III-4) is a 62-year-old woman who complained of night blindness when she was approximately 20 years of age. She underwent an ophthalmologic examination, and was clinically diagnosed with retinitis pigmentosa. In a recent examination, visual acuity was recorded at 20/40 in the right eye and 20/30 in the left. Visual field (Humphrey Field Analyzer testing) was found to be concentrically reduced with the retention of a central island vision of almost 15°. Both rod and cone electroretinographic responses were acutely abnormal. Fundus examination revealed, in both eyes, a diffused atrophy of the retinal pigment epithelium with midperipheral bone-spicule pigment deposits and a narrowing of retinal arterioles. In both eyes a pale optic disk and a large area of sharply demarcated chorioretinal atrophy in the macular area could be identified (Fig. 2).

Patient IV-1, daughter of the above patient, is a 38-year-old woman who complained of mild metamorphopsias in both eyes. At the ophthalmologic examination, her visual

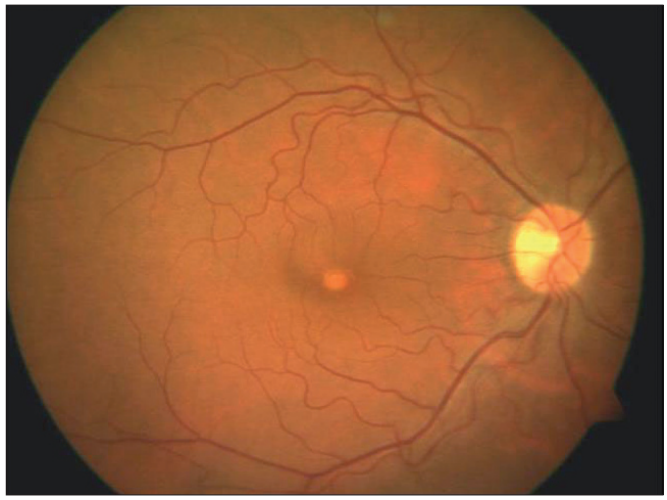

Fig. 3 - *Posterior pole of Patient IV-1 with yellowish round deposits in the macular area.*

acuity was 20/20 in both eyes. Visual field, electroretinographic, and electroculographic responses were within normal limits. Funduscopy demonstrated that in both eyes, in the macular area, there existed the presence of round yellowish deposits whose diameters were largely smaller than that of the optic disk (Fig. 3). OCT scans in the macular area revealed the presence of hyperreflective deposits at the level of the retinal pigment epithelium layer.

Patients I-2 and II-4 died several years ago and both were reported to have retinitis pigmentosa.

Patients III-4 and IV-1 underwent molecular genetic exa-

mination of the RDS gene. DNA samples were analyzed for mutations in all three exons of the peripherin/RDS gene by direct sequencing (3100 Genetic Analyzer) using Big Dye Terminator chemistry (Applied Biosystems, Foster City, CA).
In both patients, III-4 and IV-1, genotype analysis revealed a 874A®G transition in exon 2 of the RDS gene leading to the amino acid change of S212G.

DISCUSSION

The missense mutation S212G is located in exon 2 and the amino acid change from serine to glycine is potentially effective because the two amino acids show different chemical and physical properties: serine is a larger polar molecule with hydrophilic properties, while glycine is a small nonpolar hydrophobic aminoacid. Moreover, the stretch of 10 amino acids beginning at codon 210 appears to be important for retinal function because different mutations within this range have been associated with retinal degeneration (1, 4, 5).
Peripherin/RDS is a membrane glycoprotein observable exclusively in the outer segments of rod and cone cells. Serine position 212 is located within the D2 intradiscal loop of the protein, which has an evolutionary conserved glycosylation site that forms homophilic bonds across the disk space, thus contributing to the bend at the edge of rod and cone disks. As a consequence, mutations in the D2 loop might have damaging effects on the formation and stability of the disk membrane proteins.
S212G mutation in the RDS gene has been previously associated with a very severe retinal degeneration with the clinical phenotype of retinitis pigmentosa, but it has never been described in patients with adult onset vitelliform macular dystrophy (4). In the family under consideration, Patient III-4 exhibited the phenotype of an advanced retinitis pigmentosa complicated by a severe macular atrophy determining reduced central visual acuity. The clinical picture could also be consistent with a late stage of cone-rod dystrophy but this diagnosis was more unlikely because the early onset of night blindness, the severe abnormalities of peripheral visual field and scotopic ERG, the appearance of arteriolar narrowing, and pale optic disk on the fundus. Contrariwise, in Patient IV-1 the same mutation is associated for the first time with a milder retinal phenotype having the clinical features of vitelliform macular dystrophy. It is thus noteworthy that in the same 212 location a mutation from serine to threonine has been reported in association with the same mild phenotype (5). The amino acid change from serine to threonine is probably less effective than the change from serine to glycine because serine and threonine share similar chemical and physical properties, including the presence of a hydroxyl group in the lateral chain.
In conclusion, we report the first association of the peripherin/RDS S212G mutation with the clinical phenotype of adult onset vitelliform macular dystrophy. In the same family this mutation can be detected in a patient with retinitis pigmentosa with severe involvement of the posterior pole, therefore representing a more severe clinical picture. Two other members of the family were reported to have retinitis pigmentosa as well. Phenotypic and intrafamilial variability has already been reported for other RDS mutations (1-3). These results support the possible influence of modifier genes or environmental factors in the clinical expression of RDS gene variants. The potential role of modifier genes is suggested by some families reported in the literature (3) where the retinal degeneration phenotypes are different in male and female members (raising the possibility of an X-linked modifier gene) or in different branches of the pedigree (2).
In patients with retinal degeneration carrying peripherin/RDS mutations, the high intrafamilial variability suggests that caution should be taken both in using molecular genetic results to predict the clinical course of the disease and in offering genetic counseling.

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