

ONLINE MUTATION REPORT

Molecular genetics of autosomal dominant retinitis pigmentosa (ADRP): a comprehensive study of 43 Italian families

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Retinitis pigmentosa is the most common form of retinal degeneration and is heterogeneous both clinically and genetically. The autosomal dominant forms (ADRP) can be caused by mutations in 12 different genes. This report describes the first simultaneous mutation analysis of all the known ADRP genes in the same population, represented by 43 Italian families. This analysis allowed the identification of causative mutations in 12 of the families (28% of the total). Seven different mutations were identified, two of which are novel (458delC and 6901C→T (P2301S), in the *CRX* and *PRPF8* genes, respectively). Several novel polymorphisms leading to amino acid changes in the *FSCN2*, *NRL*, *IMPDH1*, and *RPI* genes were also identified. Analysis of gene prevalences indicates that the relative involvement of the *RHO* and the *RDS* genes in the pathogenesis of ADRP is less in Italy than in US and UK populations. As causative mutations were not found in over 70% of the families analysed, this study suggests the presence of further novel genes or sequence elements involved in the pathogenesis of ADRP.

Retinitis pigmentosa is a clinically and genetically heterogeneous type of retinal degeneration which results in progressive loss of vision. It is characterised by abnormalities of the photoreceptors or the retinal pigment epithelium. Patients with this disorder typically develop night blindness, followed by constriction of the peripheral visual fields, bone spicule-like pigmentary deposits, and abnormal electroretinography (ERG). In the more advanced stages of the disease, there are intraretinal and preretinal clumps of black melanin pigment, attenuated retinal vessels, loss of retinal pigment epithelium, and pallor of the optic nerve.¹ The time of onset of the disease varies from childhood to middle age.² The incidence is estimated to be 1 in 4000–5000 people in Western populations.^{3–4} Inheritance can be autosomal dominant, autosomal recessive, X linked, or in rare cases as a digenic trait. However, in the majority of cases (about 50–60% in the white population) it is impossible to establish the pattern of inheritance, and these cases are defined as “sporadic.”^{5–7}

Autosomal dominant retinitis pigmentosa (ADRP) represents between 15% and 35% of all cases of the disorder, depending on the countries and the ethnic groups analysed, with the highest values being found in the USA⁸ and the lowest in southern Europe.⁹ A previous study reported that the prevalence of ADRP in the Italian population is about 17%,¹⁰ which is concordant with estimates from other studies carried out in southern Europe.⁹ To date, 12 genes have been

clearly associated with the pathogenesis of this condition (RETnet, <http://www.sph.uth.tmc.edu/Retnet/disease.htm>). The rhodopsin (*RHO*) gene is the most commonly involved in ADRP (25–50% of cases) followed by *RPI* (5–10%), *RDS* (5%), and *IMPDH1* (5–10%). These prevalence values were all derived from different and heterogeneous studies mostly carried out in American and British populations,^{6–11–12} and a simultaneous analysis on all the 12 ADRP genes in a homogeneous population was never reported. In addition, fewer molecular studies have been carried out in non-British European patients with retinitis pigmentosa¹³ and no data at all are available for the Italian population.

Here, we describe the first comprehensive mutational analysis for all the currently known ADRP genes in the same population—that is, in a well characterised set of Italian ADRP families. We were able to detect causative mutations in approximately one third of the families analysed. The prevalences and the type of mutations identified indicate that the genetic epidemiology of ADRP in Italy, and possibly in southern Europe, is different from that reported in American and British populations.

METHODS

Patients

ADRP families were recruited from northern, central, and southern Italy. Informed consent was obtained from all adult subjects enrolled in the study. The six ophthalmological centres that participated in the study used the same protocols for the clinical diagnosis and the classification of patients. Only families showing a well defined autosomal pattern of inheritance were selected (n=43)—in particular those characterised by the presence of at least two affected generations and male to male transmission. The ophthalmological examination included the best corrected visual acuity with the Snellen visual chart, slit lamp biomicroscopy, fundus examination, Goldmann kinetic visual field examination, and electroretinography. The ERG was recorded by means of corneal contact lens electrodes with a Ganzfield stimulator according to international clinical standards.

Mutation analyses

Genomic DNA was extracted from blood samples employing standard techniques¹⁴ and amplified by polymerase chain reaction (PCR) using oligonucleotide primer pairs that amplify the coding exons as well as the intron–exon junctions of the ADRP genes selected for this study. The sequences of the primers and the PCR conditions were as previously described^{15–26} and are summarised in supplementary table 1, which can be viewed on the JMG website (<http://www.jmedgenet.com>).

Abbreviations: ADRP, autosomal dominant retinitis pigmentosa; dHPLC, denaturing high performance liquid chromatography

Table 1 Summary of autosomal dominant retinitis pigmentosa mutations identified

Gene	Nucleotide change	Amino acid change	Type of mutation	Exon	Number of families	Relative frequency
<i>RP1</i>	2029C→T	R677X	Nonsense	4	2	4.6%
<i>RHO</i>	403C→T	R135W	Missense	2	4	9.3%
	1040C→T	P347L	Missense	5	2	4.6%
	499T→C	C167R		2	1	2.3%
<i>NRL</i>	152C→T	P51L	Missense	2	1	2.3%
<i>CRX</i>	458delC	P153fs	Frameshift	3	1	2.3%
<i>PRPF8</i>	6901C→T	P2301S	Missense	42	1	2.3%

www.jmedgenet.com/supplemental). In particular, we analysed all coding exons of the *RHO*, *RDS*, *RP1*, *IMPDH1*, *PRPF31*, *CRX*, *NRL*, *FSCN2*, *HPRP3*, and *RP9* genes and the exons harbouring the previously identified mutations of the *CA4* and *PRPF8* genes, namely exons 1 and 42.^{23–25} This analysis was carried out in one patient per family. Amplified products underwent denaturing high performance liquid chromatography (dHPLC) analysis. All products displaying a dHPLC pattern different from controls were sequenced, using the ABI PRISM Big Dye terminator cycle sequencing V2.0 kit, and the reactions were analysed with an ABI-PRISM 3100 genetic analyser (Applied Biosystems, Foster City, California, USA). All the identified sequence variants leading to amino acid missense variations were first tested in the other members of the family, both affected and unaffected, to verify whether or not they segregated with the retinitis pigmentosa phenotype. If segregating with the disease, the sequence variants were also tested in at least 100 control chromosomes by dHPLC analysis. The *CRX* 458delC variation that led to a premature truncation of the *CRX* protein was not tested in control samples.

RESULTS AND DISCUSSION

Family selection and clinical studies

We selected for this analysis 43 Italian ADRP families (237 affected individuals in all) from a pool of about 600 families with retinitis pigmentosa. The age of disease onset in these cases ranged from 3 to 55 years (mean (SD), 15 (13.6) years; mean disease duration, 26.5 (15) years). The mean best corrected visual acuity was 20/50 (ranging from 20/20 to light perception). The ophthalmoscopic appearances were typical retinitis pigmentosa in 59.3% of cases, and atypical in 40.7% (no pigment, 4.8%; sector involvement, 12.5%; pericentral involvement, 3.3%). Electroretinographic scotopic and photopic responses were extinguished in 71.6% of the patients, while a scotopic and photopic ERG was recordable in 11.5% and 16.9%, respectively.

The non-biased geographical distribution of these families throughout Italy and a standardised clinical evaluation (see Methods) ensured that this sample was truly representative of the ADRP population in Italy. Based on previous reports,¹⁰ and on our preliminary data on the epidemiology of retinitis pigmentosa in Italy (unpublished data), we estimated that the prevalence of ADRP in Italy constitutes approximately 17% of the entire population of people with the disease. If we assume that the incidence of retinitis pigmentosa in Italy is 1/4000, the sample of ADRP patients recruited in this study should amount to about 10% of the entire Italian ADRP population and therefore represents a valid subset to assess the relative prevalences of the known retinitis pigmentosa genes in the pathogenesis of ADRP in Italy.

Mutation analyses

We carried out mutation analysis in the selected families on the 12 genes that have been clearly shown to be responsible

for ADRP (see Methods and supplementary table 1). We identified the causative mutation in 12 of the 43 families analysed (28%) (table 1). Overall, we detected seven different mutations, two of which represent new mutations. The *RHO* gene was mutated in seven families (16% of cases), with three different mutations identified. The R135W missense mutation (403C→T at the nucleotide level) represents the most frequent mutation in our set, as it was found in four families (9% of the total and 57% of all *RHO* mutations). Two other mutations were found in more than one family, namely the *RHO* P347L and the *RP1* R677X (1040C→T and 2029C→T, respectively, at the nucleotide level).

Two new mutations were identified in this study, one in *CRX* and one in *PRPF8*. The novel *CRX* mutation was represented by the deletion of a cytosine at nucleotide position 458 (458delC) which leads to a premature truncation of the *CRX* protein at position 153 (P153fs). Patients harbouring this mutation have retinitis pigmentosa with macular dystrophy and extinguished ERG, which is consistent with the previously described ADRP phenotypes caused by *CRX* mutations.^{11–27} On the other hand, the novel *PRPF8* mutation was a substitution of a cytosine with a thymine at nucleotide position 6901 (6901C→T) which leads to the substitution of the proline in position 2301 of the *PRPF8* predicted protein with a serine (P2301S). This mutation represents the seventh missense mutation identified in the *PRPF8* gene so far. This suggests that the nucleotide at position 6901 of the *PRPF8* coding sequence is a sensitive site for mutations, as it was already found to be the target of an ADRP missense mutation by McKie *et al* (namely 6901C→A, leading to P2301T).²⁸

As expected, the severity of the clinical phenotype in the families carrying the identified mutations could be related to the mutated gene. For example, in all the patients with *RHO* mutations, we observed a more severe phenotype. The patients had early onset of disease, retained central visual acuity until the second decade of life, had concentric isoptere shrinkage of up to 10° in the centre at the Goldmann kinetic visual field examination, and had extinguished electroretinograms in the early stages of the disease. On the other hand—as also previously described¹⁵—the clinical phenotype

Table 2 Novel single nucleotide polymorphisms leading to amino acid variations identified in autosomal dominant retinitis pigmentosa genes

Gene	Nucleotide change	Amino acid change
<i>IMPDH1</i>	1142A→G	H381R
<i>NRL</i>	199C→T	P67S
<i>FSCN2</i>	412C→T	H138Y
<i>RP1</i>	5448C→A	C1816X
<i>RP1</i>	1380G→C	K460N
<i>RP1</i>	4735T→G	L1579V
<i>RP1</i>	1705A→G	T569A

associated with *RP1* gene mutations was less severe with a late onset of disease, after the third decade of life. The patients retained good visual acuity and recordable rod and cone ERG signals until the start of the fourth decade.

Identification of novel polymorphisms

We also found novel single nucleotide polymorphisms in some of the genes analysed (*RP1*, *IMPDH1*, *NRL*, and *FSCN2*) that caused amino acid substitutions (table 2). In particular, the *RP1* gene has a significantly high frequency of missense variations with no pathogenic significance. Interestingly, one of these sequence variants, 5448C→A, which determines a premature truncation of the RP1 protein at amino acid position 1816 (C1816X), was found in the homozygous state in an unaffected relative of an ADRP patient. It was previously reported that premature truncations of the RP1 protein in the C-terminal part (R1933X) were not involved in the retinitis pigmentosa pathogenesis.²⁹ Our data not only extend to the amino acid position 1816 the N-terminal border for non-pathogenic sequence variations in RP1 but also suggest that most of the 340 C-terminal amino acids of this protein are not endowed with an important function, because their complete loss in homozygosity is apparently well tolerated and not associated with any abnormal phenotype. This hypothesis is also confirmed by the low conservation across evolution of this portion of the RP1 protein. We also found sequence variations in the *NRL*, *IMPDH1*, and *FSCN2* genes that lead to non-conservative amino acid variations and affect amino acids that are significantly conserved in evolution. However, none of these variants was found to segregate with the retinitis pigmentosa phenotype in the families analysed, indicating that they are polymorphisms and not causative of the retinitis pigmentosa mutation. In particular, the P67S sequence variant in *NRL* is of particular interest because it affects an amino acid residue that is highly conserved across evolution (it is present even in the chicken and in *Xenopus laevis*) and because of the very low occurrence of sequence variations in the *NRL* gene.³⁰ We did not detect this variation in more than 400 additional chromosomes analysed, suggesting that it is a rare polymorphism. It will be important to determine whether this sequence variation predisposes to retinitis pigmentosa or to other eye phenotypes.

Relative gene prevalence in Italian ADRP

The frequency of the involvement of the 12 genes analysed in these Italian ADRP families is reported in table 1 and fig 1. As expected, *RHO* is the gene most commonly involved in ADRP pathogenesis, as causative mutations were found in 16% of families. However, this prevalence is less than the 25–50% range reported in the USA and the United Kingdom,^{11–12} and

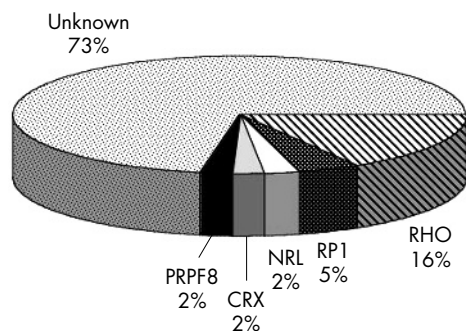


Figure 1 Classification of the families with autosomal dominant retinitis pigmentosa, based on the results of the mutation analyses.

is more similar to that described in other populations from southern Europe—for example, Spain and southern France^{13–31}—and in the Far East.^{13–32–33} The most common *RHO* mutation identified was the R135W (present in four families) followed by the P347L (in two families). On the other hand, the P23H mutation, which is the most common one found in the USA, was not detected in our sample, and this is consistent with previous studies carried out in other European populations.^{34–35}

Two families were mutated in the *RP1* gene, which therefore represents, after *RHO*, the gene most commonly responsible for ADRP in Italy. The other genes mutated in ADRP families were *CRX*, *NRL*, and *PRPF8* (table 1). No mutations were detected in *RDS*, *IMPDH1*, and *PRPF31*, which together account for about 15% of ADRP in non-Italian populations (RETNET, <http://www.sph.uth.tmc.edu/Retnet/disease.htm>). Altogether, these findings confirm that retinitis pigmentosa pathogenesis is very variable in different populations.

We did not identify causative mutations in any of the 12 ADRP genes screened in over 70% of the families analysed ($n = 31$; fig 1). Thus the pathogenesis of the majority of ADRP families in Italy is not accounted for by mutations in the coding exons of the retinitis pigmentosa genes tested. We cannot exclude the possibility that the genes analysed in this report may nevertheless underlie retinitis pigmentosa pathogenesis in a fraction of these 31 Italian families owing to mutations residing in either unidentified exons or in regulatory elements of the analysed genes. However, our results strongly suggest the presence of additional unidentified genes that are involved in the pathogenesis of ADRP in these families, and extensive linkage analysis will be needed to discriminate between these two hypotheses.

We believe that this study, which is the first simultaneous and comprehensive clinical/molecular analysis of all the currently known ADRP genes in a well characterised set of families, will improve genetic counselling and the prognostic evaluation of retinitis pigmentosa in Italian patients, and shed further light on the molecular mechanisms underlying this complex group of disorder.

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Supplementary table 1, showing primer sequences and PCR conditions, is available on the JMG website: <http://www.jmedgenet.com/supplemental>

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