LETTER TO JMG

Dominant X linked retinitis pigmentosa is frequently accounted for by truncating mutations in exon ORF15 of the *RPGR* gene

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Retinitis pigmentosa (RP) is a group of progressive hereditary disorders of the retina in which various modes of inheritance have been described. The X linked forms of retinitis pigmentosa (XLRP, MIM 268000) are among the most severe owing to their early onset, leading to significant vision loss before the fourth decade. Five XLRP loci have been localised by linkage: RP2 (MIM 312600), RP3 (MIM 312610), RP6 (MIM 312612), RP23,[1] and RP24 (MIM 300155). The major loci, RP2 and RP3, map to Xp11.4 and Xp21.1, respectively. RP3 is accounted for by mutations in the retinitis pigmentosa GTPase regulator (*RPGR*) gene.[2] RP3 accounts for 70% of XLRP,[3 4] but until recently only 20% of mutations were identified in RP3 families, suggesting genetic heterogeneity at this locus. This hypothesis has been excluded by the discovery of a mutational hot spot in a new *RPGR* exon, ORF15.[5]

In 1997, we reported on X linked RP in nine families with constant and severe expression in carrier females.[6] In this series, onset was delayed and sometimes milder in females than in hemizygous males. However, in all the pedigrees in the present report, some females were as severely affected as

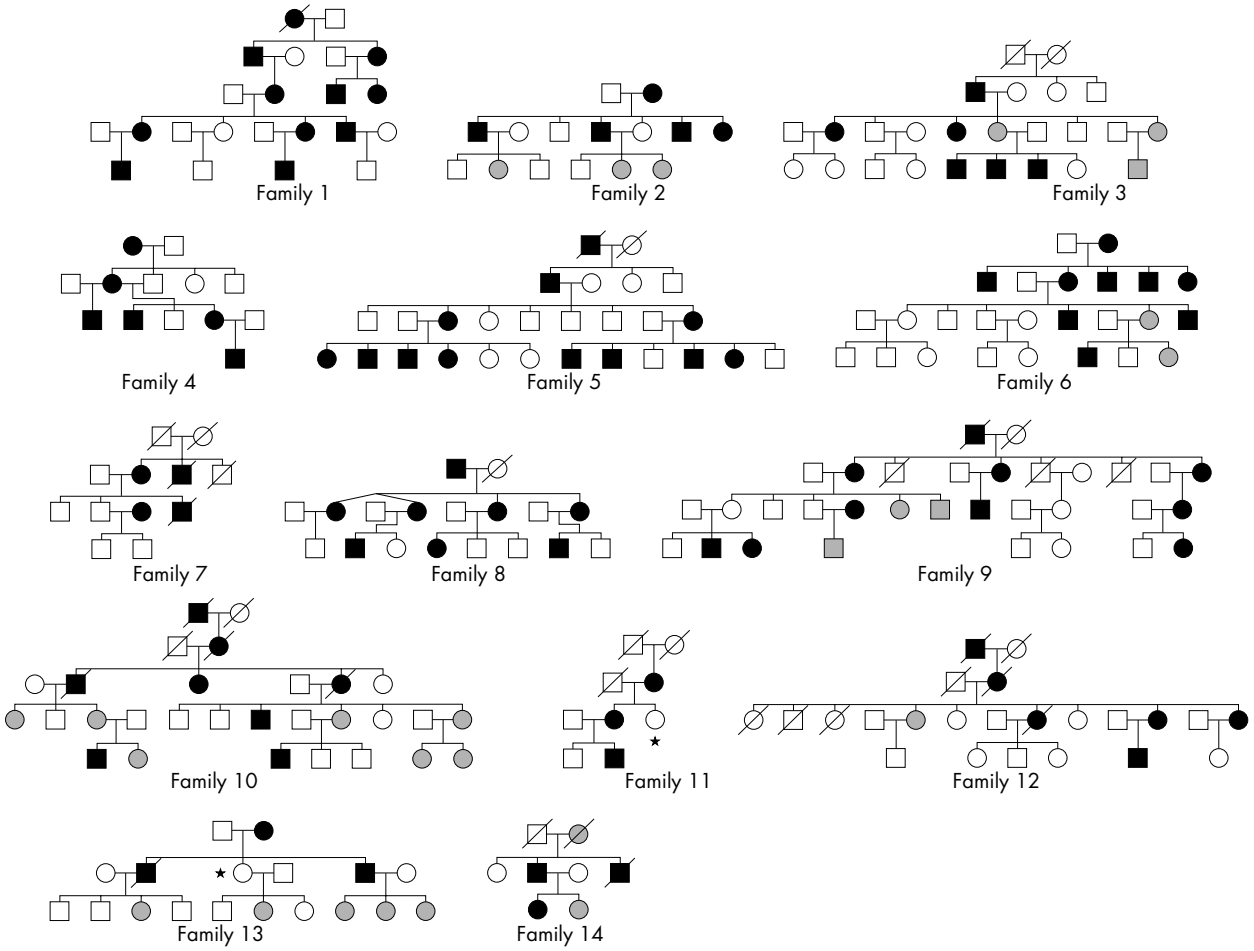

Figure 1 Pedigrees of X linked dominant RP families. Families 1 to 9 have been reported previously.[6] Women displaying retinal degeneration as severe as in the males are shown in black. Women whose clinical status is consistent with the carrier phenotype in XLRP are shown in grey. Asterisks show asymptomatic potential carriers for whom a null allele was found. The males in grey were young children when examined. They displayed severe myopia and night blindness. ERG was not performed.

Table 1 *RPGR* mutations in unrelated DXLRP families

Family	Mutation	Predicted effect
1	g.ORF15+465 G>T	p.ORF15 E155X
2	Unidentified	
3	g.ORF15+1083_1087 del 5bp	Frameshift
4	g.ORF15+930 G>T	p.ORF15 G310X
5	Unidentified	
6	g.ORF15+650_651 del AG	Frameshift
7	Unidentified	
8	Unidentified	
9	Unidentified	
10	g.ORF15+1059 G>T	p.ORF15 E353X
11	g.ORF15+481_482 del GA	Frameshift
12	g.ORF15+481_482 del GA	Frameshift
13	g.ORF15+434 del G	Frameshift
14	g.ORF15+650_651 del AG	Frameshift

males (fig 1). This form of X linked RP was therefore regarded as partially dominant (DXLRP). The disease gene was localised to chromosome Xp21 in the genetic interval encompassing the RP3 locus (Zmax = 13.71 at DXS1110), but screening of the *RPGR* gene failed to detect any mutation in these families.[6] On the other hand, it is worth noting that in 1995 McGuire *et al*[7] reported the mapping of an X linked dominant cone-rod dystrophy to chromosome Xp22.13-Xp22.11 (RP15).[7] This locus was excluded by linkage analyses in the DXLRP families of our series. However, the RP15 locus has been recently remapped at the RP3 locus,[8] strongly suggesting that the RP15 family and the DXLRP families were affected with the same disorder. RP15 was subsequently shown to be accounted for by a de novo insertion in exon ORF15 of the *RPGR* gene.[8] Along the same lines, Zhang *et al*[9] reported very recently on severe retinal atrophy in bitches carrying a heterozygous 2 bp deletion in the *RPGR* ORF15 exon.[9] These discoveries prompted us to screen this exon in the nine originally described DXLRP families (families 1-9, fig 1)[6] as well as in five additional families in which the segregation of the disease was consistent with dominant X linked inheritance (families 10-14, fig 1). Linkage analyses confirmed the localisation of the disease causing gene at the RP3 locus in these latter families (data not shown, available on request).

Direct sequencing of the *RPGR* exon ORF15 in affected patients allowed the identification of eight different null mutations in 9/14 families (table 1). The segregation of the mutation with the disease was confirmed in all nine families. Interestingly, in two of these families, the mutation was found in an asymptomatic potential carrier (families 11 and 13, fig 1).

On the other hand, in frame deletions or duplications reported previously as polymorphisms[5] were identified in 2/5 families with no mutation (748_768 del 21 bp and 1150_1170 dup 21 bp, family 2; 912_914 del GAG, family 9) and direct sequencing of the *RPGR* exon ORF15 failed to detect any base change in the three remaining families. Nevertheless, linkage analyses confirmed the localisation of the gene at the RP3 locus,[6] suggesting that in these families the disease might be caused by a mutation located in an unexplored region of the *RPGR* gene, such as the promoter or the introns.

In conclusion, we report here on the identification of null *RPGR* alleles in patients affected with DXLRP. It is worth noting that in this retinal dystrophy, both males and females display minimal inclusion criteria for RP.[6 10] Although the age at onset of the disease in females is delayed compared to males (20-40 years *v* 10-20 years, respectively) the visual impairment, the fundus alteration, and the visual field reduction can be as severe in heterozygous females as in hemizygous males. In these females whose ERG is non-recordable, no preferential X inactivation was observed.[6] It would be extremely interesting to know the exact phenotype of females harbouring truncating mutations in *RPGR* exon ORF15 in the XLRP families recently reported by Vervoort *et al*.[5] Indeed, if some of the women were more severely affected than is usually described for carrier females in recessive X linked RP (that is, tapetal-like reflex or peripheral pigmentary deposits in the fundus), we would have to consider RP3 as an incomplete dominant X linked disease such as is now reported for ornithine transcarbamylase deficiency.[11]

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