What's in a Name? *RPGR* Mutations Redefine the Genetic and Phenotypic Landscape in Retinal Degenerative Diseases

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The boundaries of once-distinct clinical entities have become blurry within the broad category of retinal and macular dystrophies as mutations in one gene can lead to diverse manifestations. In addition, individuals carrying an identical mutation, even within a family, may present an array of phenotypes. While we are still struggling to correlate clinical heterogeneity to specific mutations/variants in identified genes, genetic studies are beginning to unravel yet another level of complexity.

X-linked forms of retinitis pigmentosa (XLRP) are relatively severe with clinical, genetic, and even allelic heterogeneity. Mutations in the retinitis pigmentosa guanosine triphosphatase regulator (*RPGR*) gene account for over 70% of XLRP and are even reported in patients with divergent retinal degenerative diseases, including cone dystrophies and macular degeneration.¹ *RPGR* and its interacting proteins in the cilium have been associated with photoreceptor dysfunction/death in many syndromic diseases.² A recent study identified *RPGR* mutations in a considerable proportion of males (29 of 214 examined) with simplex retinal degeneration phenotypes.³ Mutations in another XLRP gene, *RP2*, were detected in three other patients. In this issue, Churchill et al.⁴ provide another twist to the *RPGR* saga by examining a cohort of 258 families that were initially categorized as autosomal dominant RP (adRP) based on the pedigree analysis. Of these, 95 families did not carry mutations in known adRP genes. These authors screened 56 of the 95 families that did not show male-to-male transmission. Interestingly, 20 families had mutations in *RPGR* and two others in *RP2*. Not unexpectedly, 12 of the 20 *RPGR* mutations were found in the ORF15 exon. Thus, *RPGR* mutations accounted for one-third of the families after known adRP genes had been excluded, and represented almost 8% of the adRP cohort being investigated by Churchill et al., second only to rhodopsin and equal to *PRPF31* and *PRPH2* (*RDS*).⁵ These findings have significant clinical implications as *RPGR* now occupies a prominent causative role in inherited retinopathies, exhibiting divergent clinical phenotypes and genetic spectrum.

Though clinical manifestations of the *RPGR* disease are primarily limited to the retina, it is tempting to hypothesize that common *RPGR* variants may modify the function of interacting proteins³ and generate phenotypic heterogeneity. When providing genetic diagnosis and counseling to patients with retinal dystrophies, *RPGR* screening should therefore receive serious consideration, both for identifying the primary defect and as a phenotypic modifier. Fortunately, gene-based therapy of *RPGR* disease is on the horizon.⁶

References

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