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Peripherin and the vision thing

A surprising variety of phenotypes are associated with mutations in the retinal protein, peripherin, including the possible human equivalent of the murine rds (retinal degeneration slow) strain.

RETINAL genetics is proving to be exceptionally fertile ground for those probing the mechanisms of visual transduction and retinal degeneration, especially as a growing collection of phenotypes are being associated with specific molecular defects. The classic example is rhodopsin, the archetypal G-protein-coupled photoreceptor with seven transmembrane domains, which is situated in the membranous disks packed together in the rod cells of the retina. More than 30 mutations in the rhodopsin gene are known to give rise to many, but not all, cases of autosomal dominant (ad) and one case of recessive retinitis pigmentosa (RP; reviewed in ref. 1), a group of retinal degenerative disorders characterized by photoreceptor destruction.

Although other X-linked and autosomal RP loci exist, the only other gene which has been formally associated with RP is peripherin/RDS. (This cumbersome title serves to distinguish the retinal peripherin from another human protein with the same name, and also to emphasize its homology with the murine *rds* (retinal degeneration slow) locus). Peripherin/RDS, like rhodopsin, is a transmembrane glycoprotein; but whereas rhodopsin is confined to the rod cells, peripherin/RDS is found in both rods and cones. Two papers in *Nature* in 1991 showed that peripherin mutations are also linked with dominantly inherited RP[2,3], but this still leaves most RP cases without a molecular explanation.

Further examination of the peripherin/RDS gene has turned up some rather surprising results, for as explained in three papers in the latest issue of *Nature Genetics*[4–6], defects within the peripherin gene account not only for a significant proportion of cases of adRP, but also incidences of macular dystrophy, butterfly-shaped dystrophy of the fovea, and retinitis punctata albescens. Although most of the newly found mutations are missense substitutions (see Table), two are putative null mutations, thereby allowing interesting comparisons to be made with the rds mouse.

Nichols *et al.*[4] examined a three-generation family in which 11 individuals suffered from butterfly dystrophy, which caused a loss of vision in the centre of the visual field (the fovea), associated with a spattering of large yellowish deposits at the level of the macular retinal pigment epithelium. Scrutiny of various candidate genes quickly identified a mutation within the peripherin/RDS gene (Gly167Asp), which segregated perfectly with the disease.

Newly discovered mutations in peripherin/RDS, and the associated phenotypes

Trp25stop	Retinitis punctata albescens[5]
ΔCys118	ad retinitis pigmentosa[6]
Gly167Asp	Butterfly dystrophy[4]
Arg172Glu	Macular dystrophy[6]
Arg172Trp	Macular dystrophy[6]
Tyr258stop	Macular dystrophy[6]

Wells *et al.*[6] examined 58 unrelated individuals with various forms of RP or macular degeneration and identified four distinct mutations among five people affected. One of these was an adRP patient with progressive loss of peripheral vision and, like another patient[2], has the same single amino-acid deletion (see Table); in contrast, the other three mutations occurred in patients with macular dystrophy who suffer from central vision loss but whose peripheral and night vision is unaffected. One of these mutations was a nonsense mutation in a mildly affected patient with adult vitelliform macular degeneration, which the authors suggest is a putative null allele of the peripherin/RDS gene. Strikingly, this patient also has a yellow deposit in the fovea, apparently at the level of the retinal pigment epithelium.

A key question that arises is which of these human phenotypes directly corresponds to the murine rds phenotype, caused by the insertion of a 10 kilobase fragment in the *rds* gene, probably producing a null allele. Although Wells *et al.* speculate that their premature termination mutant at residue 258 may be analogous to the rds mouse (because missense mutations or single amino-acid deletions as found in adRP are unlikely to give rise to a null allele), Kajiwara *et al.*[5] suggest a different phenotype. They too have detected a premature stop codon in the peripherin/RDS gene caused by deletion of two base pairs caused by deletion of two base pairs much earlier in the sequence, at codon 25, but in this case the patient suffers from retinitis punctata albescens. This disorder, like RP, is a progressive retinal degeneration, but it differs from RP in that yellow–white subretinal deposits are present. Although the origin of these deposits has yet to be linked conclusively with the peripherin mutation, it is tempting to speculate, in light of the amino-terminal location of the stop codon, that this putative null allele is the human equivalent of the rds mouse.

The genes for two human macular diseases (Best's disease[7,8] and North Carolina macular dystrophy[9]) have recently been mapped. However, the peripherin/RDS studies are the first documented mutations associated with this phenotype, and could prove to be a useful genetic model for a much commoner form of blindness in older people known as age-related macular degeneration. Less clear is why certain mutations give rise to such distinct patterns of retinal degeneration. It is possible that the macular degeneration mutations interfere with the dimerization of peripherin/RDS molecules, or other types of protein–protein interaction. The expression of peripherin/RDS in both rods and cones, in contrast to rhodopsin, is also likely to be significant in explaining the range of phenotypes.

The variety of phenotypes associated with peripherin/RDS abnormalities provides yet another example of the diverse results of mutations within a single gene. Other examples include the collagen II gene, which can give rise to chondrodysplasia[10] and Stickler syndrome[11], and the paired box gene, *PAX3*, defects in which cause both Waardenburg syndrome and the paediatric solid tumour, alveolar rhabdomyosarcoma[12]. **Kevin Davies**

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Also in this month's *Nature Genetics*: adenoviruses deliver genes to the brain; an improved mouse model for Lesch–Nyhan disease; mapping the gene for a hereditary form of stroke; and community screening for cystic fibrosis.

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