

our vision is
your VISION



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Summary of current research interests

Over the years we have found many novel genes causing eye disease. Current research interests include further genetic linkage studies, disease gene mapping of autosomal dominant and autosomal recessive loci through

pedigree analysis, positional cloning of novel eye disease genes, functional analysis of wild type and mutant genes and biochemical investigations of the impact of mutations on protein structure and function.

Key achievements

In the absence of any biochemical clues a reverse genetics approach allows the chromosomal localisation of the disease gene to a defined region of the human genome. For this purpose clinically well characterised large pedigrees are essential and Moorfields Eye Hospital along with a number of ophthalmic departments nationally and internationally have been central to this programme. Positional cloning has subsequently led to the identification and characterisation of many of the genes for inherited eye diseases. Such work underpins the development of novel approaches to gene or gene-based therapies.

- (1984) Nature 309: 253-255 First eye disease locus mapped using recombinant DNA technology
- (1991) Trends in Genetics 7: 5 First high throughput method for mutation detection in genes by heteroduplex analysis
- (1993) Nature Genetics 3: 213-218 First macular degeneration gene cloned-RDS
- (1994) Nature Genetics 6: 210-213 First cone-rod dystrophy (CRD) locus mapped using genetic linkage studies
- (1997) Cell 91: 543-553 First transcription factor gene (CRX) cloned for retinal degeneration
- (2000) Nat Genet 25: 15-17 First aquaporin gene (MIP) cloned for Cataract
- (2000) Nat Genet 26: 211-215 First dominant optic atrophy gene cloned-OPA1
- (2001) Mol Cell 8: 375-381 First splicing factor gene (PRPF31) cloned for autosomal dominant retinitis pigmentosa

Research Projects

1. Mapping and cloning of autosomal dominant retinitis pigmentosa (adRP) genes: We have recently mapped a large adRP family of French Canadian origin to chromosome 9. A strong candidate for this locus has been isolated and work is ongoing to confirm its involvement in adRP. Also after exclusion of all known loci for adRP, total genome linkage work is underway to map a new locus for RP in a large multi-generation family of English origin from Moorfields Eye Hospital.
2. An interesting feature of the RP11 locus on chromosome 19q is partial penetrance. The gene is a ubiquitously expressed splicing factor PRPF31. Carriers of the disease gene can be symptomatic or asymptomatic. It has been noted that expression level of PRPF31 from the wild-type allele is responsible for this unique feature. Work is ongoing to identify the genomic sequence that regulates the expression level of PRPF31 thereby either manifesting or rescuing the disease phenotype. It is anticipated that the sequence motif is close to or within 500Kb of the RP11 gene.
3. Functional characterisation of splicing factor mutations on splicing function in retinal cells. A wide variety of mutations in PRPF31 have been identified to date that include missense, deletions, insertions and splice site mutations making haplo-insufficiency as the most likely cause of the disease. A knock-in animal model has been generated which is currently under investigation to assess for signs of photoreceptor degeneration.
4. Mapping and cloning of a novel gene (RP25) for autosomal recessive retinitis pigmentosa (arRP): In close collaboration with Dr Guillermo Antinolo and colleagues, we are trying to identify the disease gene for RP25 on chromosome 6q. Seven families of Spanish origin map to this locus and recently we have identified a further three families of Chinese origin (in collaboration with Dr Calvin Pang and colleagues) mapping to the RP25 interval. The region contains over 100 genes and so far we have excluded approximately half of these genes from RP25. Work is ongoing to screen the remaining genes.



Publications [Click here for complete publications list](#)

Close genetic linkage between X linked retinitis pigmentosa and a restriction fragment length polymorphism identified by recombinant DNA probe L1.28. Bhattacharya, S.S., Wright, A.F., Clayton, J.F., Price, W.H., Phillips, C.I., McKeown, C.M.E., Jay, M.R., Bird, A.C., Pearson, P.L., Southern, E.M. and Evans, H.J. (1984): Nature, 309: 253-255.

Genetic linkage of cone-rod dystrophy to chromosome 19q and evidence for segregation distortion. Evans, E., Fryer, A.F., Inglehearn, C.F., Duvalloung, J., Whittaker, J., Gregory, C.Y., Ebenezer, N., Hunt, D. and Bhattacharya, S.S. (1994). Nature Genetics. 6: 210-213.

Cone-Rod Dystrophy due to mutations in a novel photoreceptor-specific homeobox gene (CRX) essential for maintenance of the photoreceptor. Freund, C.L., Gregory-Evans, C.Y., Furukawa, T., Papaioannou, M., Looser, J., Ploder, L., Bellingham, J., Ng, D., Herbrick, J.S., Duncan, A., Scherer, S.W., Tsui, L., Loutradis-Anagnostou, A., Jacobson, S.G., Cepko, C.L., Bhattacharya, S.S. and McInnes, R.R. (1997). Cell. 91: 543-553.

Mutation in NRL is associated with autosomal dominant retinitis pigmentosa. Bessant, D.A.R., Payne, A.M., Mitton, K.P., Wang, Q-L., Swain, P.K., Plant, C., Bird, A.C., Zack, D.J., Swaroop, A. and Bhattacharya, S.S. (1999). Nat. Genet. 21: 355-356.

Missense mutations in MIP underlie autosomal dominant 'polymorphic' and lamellar cataracts linked to 12q. Berry, V., Francis, P., Kaushal, S., Moore, A. and Bhattacharya, S. (2000). Nat. Genet. 25: 15-17.

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- British RP Society
- Special Trustees of Moorfields Eye Hospital
- European Union
- Medical Research Council
- The Wellcome Trust
- Sir Jules Thorn Trust
- Ulverscroft Foundation
- Guide Dogs for the Blind

Collaborators:

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