Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Inherited retinal disease: genetic testing and a new era of therapy

1. Summary of the impact

Research at the UCL Institute of Ophthalmology over the last 20 years has resulted in the identification of a large number of novel genes that cause inherited retinal disease. These genes have been incorporated into diagnostic tests, which have allowed molecular diagnosis, improved genetic counselling including pre-natal/pre-implantation diagnosis, better information about prognosis and have informed decisions about which diseases should be prioritised for clinical trials of novel treatments. The identification of these genes has greatly improved understanding of disease mechanisms, an essential prerequisite for developing new treatment approaches such as gene therapy.

2. Underpinning research

A remarkable number of mutations in ocular genes lead to blinding disease and the retina is particularly notable in this regard. In retinitis pigmentosa, rods are primarily affected and secondary loss of central cones leads to severe visual impairment. In other degenerations, the cones are primarily affected. Many of these conditions have an early age of onset and lead to life-long visual loss.

Professor Shomi Bhattacharya laid the foundation of ophthalmic genetics with the mapping of X-linked retinitis pigmentosa and since then he, his group, UCL colleagues (Professors Hardcastle, Moore and Webster) and collaborators have identified more genes that cause eye disease than any other centre in the world. The huge patient base at Moorfields Eye Hospital and the Hospital's role as a national referral centre for inherited eye disease, together with an extraordinary body of work defining the pedigrees of thousands of families (including 30,000 individuals) have come together to make this achievement possible. Professor Alan Bird was the early clinical lead in this work and more recently Professors Tony Moore and Andrew Webster and Mr Michel Michaelides have taken over responsibility for phenotyping and managing these patients. An internationally renowned electrodiagnostics department led by Professor Graham Holder has assisted in functional phenotyping. Electrophysiology has contributed insights into both the cellular location of the genetic defect(s) and pathogenesis.

In 1997, three labs simultaneously identified CRX, a novel homeobox gene, as a cause of cone-rod dystrophy **[1]**. Other disease-causing genes identified include NRL (1998) **[2]** PRPF31 (2001) **[3]** TOPORS (2007) **[4]** and OPA1 (2000) **[5]**. In 2008, a study described **EYS**, a major gene for autosomal recessive retinitis pigmentosa accounting for 10-15% of cases world-wide **[6]**. The UCL team has itself or in combination with other groups contributed to the identification of 20 other genes causing inherited retinal disease.

While the focus has been on monogenic disorders we have also made a major contribution to the international effort to identify the genetic variants that are associated with an increased risk of age-related macular degeneration (AMD). We, in collaboration with Cambridge University, were the first to identify a polymorphism in C3 as one of the major genetic variants predisposing to AMD **[7]** and we have been a major collaborator in an international consortium that has identified further AMD genes.

Flowing from this discovery we have run two interlocking strands of research. First, we have advanced our understanding of pathogenesis with extensive programmes involving in vitro and animal model studies. Second, having identified in the mid 1990s the potential for gene therapy we have, under Professor Robin Ali's leadership, developed the technology for gene therapy of eye disease. This has led to the first demonstration that gene therapy can improve retinal function in

human inherited retinal disease **[8]**.

3. References to the research

[1] Freund CL, Gregory-Evans CY, Furukawa T, Papaioannou M, Looser J, Ploder L, Bellingham J, Ng D, Herbrick JA, Duncan A, Scherer SW, Tsui LC, Loutradis-Anagnostou A, Jacobson SG, Cepko CL, Bhattacharya SS, McInnes RR. Cone-rod dystrophy due to mutations in a novel photoreceptor-specific homeobox gene (CRX) essential for maintenance of the photoreceptor. Cell. 1997 Nov14;91(4):543-53. http://dx.doi.org/10.1016/S0092-8674(00)80440-7

[2] Bessant DA, Payne AM, Mitton KP, Wang QL, Swain PK, Plant C, Bird AC, Zack DJ, Swaroop A, Bhattacharya SS. A mutation in NRL is associated with autosomal dominant retinitis pigmentosa. Nat Genet. 1999 Apr;21(4):355-6. http://dx.doi.org/10.1038/7678

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[4] Chakarova CF, Papaioannou MG, Khanna H, Lopez I, Waseem N, Shah A, Theis T, Friedman J, Maubaret C, Bujakowska K, Veraitch B, Abd El-Aziz MM, Prescott de Q, Parapuram SK, Bickmore WA, Munro PM, Gal A, Hamel CP, Marigo V, Ponting CP, Wissinger B, Zrenner E, Matter K, Swaroop A, Koenekoop RK, Bhattacharya SS. Mutations in TOPORS cause autosomal dominant retinitis pigmentosa with perivascular retinal pigment epithelium atrophy. Am J Hum Genet. 2007 Nov;81(5):1098-103. http://dx.doi.org/10.1086/521953

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[6] Abd El-Aziz MM, Barragan I, O'Driscoll CA, Goodstadt L, Prigmore E, Borrego S, Mena M, Pieras JI, El-Ashry MF, Safieh LA, Shah A, Cheetham ME, Carter NP, Chakarova C, Ponting CP, Bhattacharya SS, Antinolo G. EYS, encoding an ortholog of Drosophila spacemaker, is mutated in autosomal recessive retinitis pigmentosa. Nat Genet. 2008 Nov; 40(11): 1285-7. http://dx.doi.org/10.1038/ng.241

[7] Yates JR, Sepp T, Matharu BK, Khan JC, Thurlby DA, Shahid H, Clayton DG, Hayward C, Morgan J, Wright AF, Armbrecht AM, Dhillon B, Deary IJ, Redmond E, Bird AC, Moore AT; Genetic Factors in AMD Study Group. Complement C3 variant and the risk of age-related macular degeneration. N Engl J Med. 2007 Aug 9;357(6):553-61. http://dx.doi.org/10.1056/NEJMoa072618

[8] Bainbridge JW, Smith AJ, Barker SS, Robbie S, Henderson R, Balaggan K, Viswanathan A, Holder GE, Stockman A, Tyler N, Petersen-Jones S, Bhattacharya SS, Thrasher AJ, Fitzke FW, Carter BJ, Rubin GS, Moore AT, Ali RR. Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med. 2008; 358 :2231-9. http://dx.doi.org/10.1056/NEJMoa0802268.

4. Details of the impact

Inherited retinal degenerations

The inherited retinal dystrophies affect about 1 in 3,000 individuals and include retinitis pigmentosa and cone-rod dystrophies. These disorders are caused by mutations in a very large number of genes. There are some non-progressive conditions but the majority progress relentlessly with currently no effective therapy. The personal and societal impact of what in many instances is life-

long visual impairment is substantial.

The research described above has made a substantial contribution to the overall body of knowledge of the genetics of eye disease and how that impacts on the lives of patients. Although our ability to treat is, as yet, limited, there are very real benefits to accurate genetic testing and associated counselling. As outlined in guidelines from the American Academy of Ophthalmology on genetic testing of inherited eye disease, "*Genetic testing can make a very positive impact on individuals and families affected with inherited eye disease in a number of ways. When properly performed, interpreted, and acted on, genetic tests can improve the accuracy of diagnoses and prognoses, can improve the accuracy of genetic counseling, can reduce the risk of disease occurrence or recurrence in families at risk, and can facilitate the development and delivery of mechanism-specific care*" **[a]**. Guidelines such as this all support the benefits of genetic testing for patients thought to have eye disease inherited in a broadly Mendelian fashion. It is important to note that the underpinning research cited above has also defined important phenotypical characteristics of these diseases, both in terms of appearances of the back of the eye and electrophysiology. All of this comes together to improve diagnostic accuracy for patients. This in turn leads to improved genetic counselling (including prenatal and pre-implantation diagnosis) and better information about long-term prognosis. This is only possible when the genetic cause of disease in an individual patient is known. Our research has identified a large number of genes that are associated with inherited retinal disease and has made such clinical advances possible.

Laboratories around the world now offer genetic testing for eye disease. For example, the US National Eye Institute created the eyeGENE Network to provide US patients with access to genetic testing for eye disease. Many of the tests offered include genes identified through our research **[b]**. In the UK, tests for genes we identified are offered by (among others) Asper Biotech, the North West Regional Genetics Service, Manchester and the Yorkshire Regional Genetics Service, Leeds **[c]**. From 2008-13 just at Moorfields, 4,952 patients have had genetic testing and counselling. A study we conducted in 2013 confirmed the overall benefits of genetic testing for retinal disease **[d]**.

AMD Testing

Age-related macular degeneration (AMD) is the commonest cause of blindness registration in the UK and presents an escalating burden given the expanding elderly population in western societies. The C3 polymorphism we identified (ref [6] above) is currently used in diagnostic tests marketed by Arctic Dx and Sequenom **[e]**. The value of this polymorphism is indicated by a recent US challenge concerning its use for diagnostic purposes (Patent Interference No 105,897) **[f]**. The recent report that inhibition of the complement pathway may alter the rate of progression of geographic atrophy, one of the blinding manifestations of AMD, makes the importance of testing of the genetics of the complement pathway even more important, as it may be amenable to therapeutic intervention.

Gene Therapy

Our fundamental studies of gene therapy have led to the first gene therapy treatment of patients with retinal degeneration. Our studies, and those of other groups in the USA, are showing that this approach can bring benefit and, although the number of patients treated to date is small, the hope that these advances have brought is colossal. The then Minister of State for Public Health described the trial as: "*a major achievement for British science and the NHS [which] shows we truly are at the forefront of innovation*" **[g]**. We have established a new era of therapeutics, not only for inherited eye disease but also for acquired conditions. These initiatives have also brought investment into the UK through our partnership with Targeted Genetics Corporation (Seattle). The transformational studies have captured the imagination of the scientific community, the media and politicians alike. The substantial coverage our trial received has helped build the UK's reputation for gene therapy and our collaborator Oxford Biomedica has recently embarked on a major programme of ophthalmic gene therapy following substantial investment from Sanofi **[h]**. Genzyme, using similar technology to that used in our early studies, are currently running a trial of gene therapy for age-related macular degeneration **[i]**.

5. Sources to corroborate the impact

[a] Genetic testing for inherited eye disease USA (2012) http://one.aao.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d

[b] http://www.nei.nih.gov/eyegene/genes_eyegene.asp

[c] See summary in report from the PHG Foundation: Genetic ophthalmology in focus, a needs assessment and review of specialist services for genetic eye disorders. (2008) http://www.phgfoundation.org/file/4199 p.39-40
And the Royal College of Ophthalmologists' briefing on *Genetic testing and counselling in inherited eye disease*. (Copy available on request.)

[d] Combs R, McAllister M, Payne K, Lowndes J, Devery S, Webster AR, Downes SM, Moore AT, Ramsden S, Black G, Hall G. Understanding the impact of genetic testing for inherited retinal dystrophy. Eur J Hum Genet. 2013 Nov;21(11):1209-13. http://dx.doi.org/10.1038/ejhg.2013.19.

[e] http://www.macularisk.com; http://laboratories.sequenom.com/retnagene-amd-seeing-risk-it-becomes-reality

[f] Patents relating to genetic markers associated with age-related macular degeneration (both patents cite study [7] above):
http://www.google.com/patents/US20090111708
http://www.google.com/patents/US8114592
Patent Interference No 105,897
http://e-foia.uspto.gov/Foia/ReterivePdf?system=BPAI&flNm=fd105897-08-16-2013-1

[g] Independent Newspaper Article (2008) http://www.independent.co.uk/life-style/health-and-families/health-news/the-blind-man-who-was-given-the-gift-of-sight-by-gene-therapy-816629.html

[h] Press release, Oxford Biomedica and Sanofi-Aventis (2009)
http://www.oxfordbiomedica.co.uk/press-releases/oxford-biomedica-and-sanofi-aventis-enter-new-collaboration-to-develop-gene-based-treatments-for-ocular-diseases/

[i] http://clinicaltrials.gov/show/NCT01024998