Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Genetic risk assessment for age-related macular degeneration

1. Summary of the impact (indicative maximum 100 words)

Age-related macular degeneration (AMD) is the most common cause of blindness in Western populations and reduces the quality of life of tens of millions of older people worldwide. In 2007 a research group at Cambridge University led by Professor John Yates in the Cambridge Institute for Medical Research discovered that a common genetic variant in the complement C3 gene was associated with an increased risk for AMD. This finding is now being used in a genetic test in North America and Europe to estimate individual risks for AMD. Those found to be at high risk are offered regular eye examinations to detect early development of the wet form of the disease before symptoms arise. This can be treated with anti-VEGF therapy. Early treatment gives the best chance of preserving sight by preventing irreversible damage to the retina.

2. Underpinning research (indicative maximum 500 words)

The research was led by Professor John Yates (Department of Medical Genetics, University of Cambridge, since 1987) who was the Principle Investigator. Key collaborators were Professor Tony Moore (UCL Institute of Ophthalmology) and Professor Alan Wright (MRC Human Genetics Unit, Edinburgh). The research was carried out, between 2001 – 2008, with funding from a Medical Research Council programme grant on which Professor Yates was the lead applicant.

Age-related macular degeneration (AMD) is a major cause of blindness. Susceptibility is influenced by age, genetic and environmental factors. Initial efforts were directed at recruiting cases of AMD and controls for genetic association studies. Later in the project, extensive genetic studies were carried out. Because complement activation had been implicated in the pathogenesis of AMD, genetic studies focused on variants in complement regulators and other complement pathway genes. This led in 2007 to the discovery, by Yates et al. of an association between AMD and a variant in the complement C3 gene which was reported in the *New England Journal of Medicine* (3). In this study 13 single nucleotide polymorphisms spanning the complement C3 and C5 genes were tested for association with AMD in 603 cases and 350 controls from the South East of England. All subjects were examined by an ophthalmologist and had independent grading of fundus photographs to confirm their disease status. To test for replication of the most significant findings, a second set of Scottish cases (244) and controls (351) were genotyped. The common functional polymorphism rs2230199 (Arg80Gly) in the C3 gene, corresponding to the electrophoretic variants C3S (slow) and C3F (fast), was strongly associated with AMD in both the English sample ($P = 5.9 \times 10^{-5}$) and the Scottish sample ($P = 5.0 \times 10^{-5}$). Compared with C3 S/S homozygotes, the odds ratio for AMD was 1.7 (CI 1.3 – 2.1) in S/F heterozygotes and 2.6 (CI 1.6 – 4.1) in F/F homozygotes. This provided strong evidence that C3, and the complement pathway, were important in the pathogenesis of AMD.

The association between C3 rs2230199 and AMD has been confirmed by several independent reports. A recent meta-analysis of all the available data carried out by other researchers has reported an effect size for this association which is very similar to our original report (Thakkinstian et al, J Epidemiol 2012). Genotyping of this variant and other genetic variants associated with susceptibility to AMD is now being used to identify individuals at increased risk of developing the disease as described below.

Other investigations undertaken as part of this programme of research confirmed the importance of smoking and family history as risk factors for AMD (1, 4) and provided additional information about the influence of the Y402H variant in the complement factor H gene on AMD susceptibility (2). A genome-wide association study which was carried out in 2007 as part of this research lead to the identification of novel AMD associated variants in the TNXB-FKBPL-NOTCH4 region of chromosome 6p21.3 (5) and these data were contributed to a GWAS meta-analysis that identified seven new AMD associated loci (6).

The key researchers contributing to this discovery were:

- Professor John Yates, Professor of Medical Genetics, Cambridge Institute for Medical Research and Department of Medical Genetics, University of Cambridge (1987 – 2008)

- Dr Tiina Sepp, Research Associate, Cambridge Institute for Medical Research and Department of Medical Genetics, University of Cambridge (2002 – 2007).
- Professor David Clayton, Professor of Statistical Genetics, Cambridge Institute for Medical Research and Department of Medical Genetics, University of Cambridge (2000 – 2012)
- Professor Anthony T Moore, Professor of Ophthalmology, UCL Institute of Ophthalmology, London
- Professor Alan Wright, Medical Research Council Human Genetics Unit, Edinburgh

3. References to the research (indicative maximum of six references)

(1) Khan JC, Thurlby DA, Shahid H, Clayton DG, Yates JRW, Bradley M, Moore AT, Bird AC for the Genetic Factors in AMD Study. Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. British Journal of Ophthalmology, 2006;90:75-80.

(2) Sepp T, Khan JC, Thurlby DA, Shahid H, Clayton DG, Moore AT, Bird AC, Yates JRW and the Genetic Factors in AMD Study Group. Complement factor H variant Y402H is a major risk determinant for geographic atrophy and choroidal neovascularisation in smokers and non-smokers. Investigative Ophthalmology and Visual Science, 2006;47:536-40.

(3) Yates JRW, 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 for the Genetic Factors in AMD Study Group. Complement C3 variant and the risk of age-related macular degeneration. New England Journal of Medicine, 2007;357:553-61.(4) Shahid H, Khan JC, Sepp T, Matharu BK, Cipriani V, Bunce C, Harding SP, Clayton DG, Moore AT, Yates JRW, for the Genetic Factors in AMD Study Group. Age-related macular degeneration: the importance of family history as a risk factor. British Journal of Ophthalmology 2012;96:427-31.

(5) Cipriani V, Leung HT, Plagnol V, Bunce C, Khan JC, Shahid H, Moore AT, Harding SP, Bishop PN, Hayward C, Campbell S, Armbrecht AM, Dhillon B, Deary IJ, Campbell H, Dunlop M, Dominiczak AF, Mann SS, Jenkins SA, Webster AR, Bird AC, Lathrop M, Zelenika D, Souied EH, Sahel JA, Léveillard T; French AMD Investigators, Cree AJ, Gibson J, Ennis S, Lotery AJ, Wright AF, Clayton DG, Yates JRW. Genome-wide association study of age-related macular degeneration identifies associated variants in the TNXB-FKBPL-NOTCH4 region of chromosome 6p21.3. Human Molecular Genetics 2012;21:4138-50.

(6) The AMD Gene Consortium, Fritsche LG*, Chen W*, Schu M*, Yaspan BL*, Yu Y*, Thorleifsson G, Zack DJ, Arakawa S, Cipriani V, Ripke S, Igo RP Jr, Buitendijk GH, Sim X, Weeks DE, Guymer RH, Merriam JE, Francis PJ, Hannum G, Agarwal A, Armbrecht AM, Audo I, Aung T, Barile GR, Benchaboune M, Bird AC, Bishop PN, Branham KE, Brooks M, Brucker AJ, Cade WH, Cain MS, Campochiaro PA, Chan CC, Cheng CY, Chew EY, Chin KA, Chowers I, Clayton DG, Cojocaru R, Conley YP, Cornes BK, Daly MJ, Dhillon B, Edwards AO, Evangelou E, Fagerness J, Ferreyra HA, Friedman JS, Geirsdottir A, George RJ, Gieger C, Gupta N, Hagstrom SA, Harding SP, Haritoglou C, Heckenlively JR, Holz FG, Hughes G, Ioannidis JP, Ishibashi T, Joseph P, Jun G, Kamatani Y, Katsanis N, N Keilhauer C, Khan JC, Kim IK, Kiyohara Y, Klein BE, Klein R, Kovach JL, Kozak I, Lee CJ, Lee KE, Lichtner P, Lotery AJ, Meitinger T, Mitchell P, Mohand-Saïd S, Moore AT, Morgan DJ, Morrison MA, Myers CE, Naj AC, Nakamura Y, Okada Y, Orlin A, Ortube MC, Othman MI, Pappas C, Park KH, Pauer GJ, Peachey NS, Poch O, Priya RR, Reynolds R, Richardson AJ, Ripp R, Rudolph G, Ryu E, Sahel JA, Schaumberg DA, Scholl HP, Schwartz SG, Scott WK, Shahid H, Sigurdsson H, Silvestri G, Sivakumaran TA, Smith RT, Sobrin L, Souied EH, Stambolian DE, Stefansson H, Sturgill-Short GM, Takahashi A, Tosakulwong N, Truitt BJ, Tsironi EE, Uitterlinden AG, van Duijn CM, Vijaya L, Vingerling JR, Vithana EN, Webster AR, Wichmann HE, Winkler TW, Wong TY, Wright AF, Zelenika D, Zhang M, Zhao L, Zhang K, Klein ML, Hageman GS, Lathrop GM, Stefansson K, Allikmets R**, Baird PN**, Gorin MB**, Wang JJ**, Klaver CC**, Seddon JM**, Pericak-Vance MA**, Iyengar SK**, Yates JRW**, Swaroop A**, Weber BH**, Kubo M**, Deangelis MM**, Léveillard T**, Thorsteinsdottir U**, Haines JL**, Farrer LA**, Heid IM**, Abecasis GR**. Seven

new loci associated with age-related macular degeneration. Nature Genetics 2013;45:433-9.
*These authors contributed equally to this work. **These authors share senior authorship.

Funding
J.R.W. Yates, A.T. Moore, D.G. Clayton, A.C. Bird, S.S. Bhattacharya, N.E. Day. Genetic Susceptibility to Age-Related Macular Degeneration. Medical Research Council programme grant, £1.8m, 2001 – 2007. Ref G0000067.

4. Details of the impact (indicative maximum 750 words)

Age-related macular degeneration (AMD) is the most common cause of blindness in Western populations, reducing the quality of life of tens of millions of older people worldwide. It affects the central macular region of the retina causing loss of central vision which has devastating consequences, preventing patients from reading, writing, driving or even recognising faces. The macular changes develop slowly and are asymptomatic in the early stages. There are two end stage forms of the disease that affect vision, namely geographic atrophy and choroidal neovascularisation, commonly referred to as 'dry' and 'wet' AMD respectively. The wet form is more likely to cause blindness but can be treated with anti-VEGF antibody therapy. This treatment is most successful if instituted early before there is irreversible damage to the retina.

Susceptibility to AMD is influenced by several genetic variants and DNA testing can be used to determine an individual's risk of developing the disease (1). Those found to be at high risk can be offered regular eye examinations to detect early development of wet AMD. The common functional variant rs2230199 in the C3 gene discovered by Professor Yates and colleagues in 2007 has a major influence on AMD susceptibility. This variant is therefore an essential component of genetic tests to determine AMD risk and it has been included in all the AMD tests currently on the market.

Cambridge Enterprise Limited on behalf of the University of Cambridge submitted a provisional US patent application based on the C3 discovery and its potential use in a genetic test for AMD in March 2008 leading to the granting of a US patent in February 2012 (2). In July 2008 Cambridge Enterprise granted a licence to the Canadian company ArcticDx to use the finding to develop a genetic test for AMD. Their Macula Risk test (3) determines the genotypes for rs2230199 and three other variants which together with smoking status are used to assign an individual to one of five risk categories for AMD. The test was launched in North America in 2009 and subsequently in Europe and India.

AMD is a major public health problem and all the more so as the elderly population grows. As a measure of the magnitude of the issue, it has been estimated that in Europe and North America some 10,000 individuals progress from dry to wet AMD every day. It has been shown that genetic variants determining susceptibility to AMD including rs2230199 also influence the risk of progression (4) and ArcticDx have promoted the Macula Risk test as a means of planning the management of patients who are identified by ophthalmologists, optometrists and others as having early or intermediate disease.

On their website, ArcticDx offer recommendations for the frequency and nature of follow up based on the patient's current stage of disease, age and Macular Risk test result (3). This programme, referred to as the Nashville Protocol, has been developed by a group of ophthalmologists in Tennessee and aims to make the best use of health care resources by targeting those at highest risk for intensive surveillance. Patients who go on to develop wet AMD and receive prompt treatment will have a better outcome. This should also save money since anti-VEGF therapy is expensive and most effective when given early. A health economic study carried out by ArcticDx has shown that around $300,000 per patient can be saved in those identified early in their conversion to wet AMD (5). However, independent cost benefit studies will be needed to confirm that the Nashville Protocol achieves the expected health care and resource benefits. In any event, it is likely that genetic testing for AMD susceptibility will have an important role in reducing the impact of AMD on the elderly. This breakthrough has generated considerable public interest and been welcomed by organisations representing blind people (6).

ArcticDx reports that 3,500 health care professionals were using the Macula Risk test as of April, 2013 with over 50,000 tests carried out (5). Utilization of the test is increasing by 30% every quarter. In the USA the test is covered by most insurance providers, including Medicare, for the ICD-9 diagnostic codes 362.50 (non-specific AMD), 362.51 (non-exudative senile macular

degeneration), 362.52 (exudative senile macular degeneration) and 362.57 (drusen). To meet the demand for the Macular Risk test in the USA, a new $1.9m molecular genetics laboratory employing 6 full-time staff has been opened in Grand Rapids, Michigan by the company ArcticAx US Ltd, an offshoot of Toronto-based ArcticDx. Cambridge Enterprise Ltd is benefitting from the licence fees received from ArcticDx and has recovered all patenting expenses and is entitled to a royalty revenue stream that is expected to exceed £1m in 2013 (5).

ArcticDx has recently launched the Macular Risk PGx test which predicts a patient's risk of progression to advanced AMD with vision loss within 2, 5 and 10 years based on 15 genetic variants in 12 AMD associated genes (including rs2230199 in C3) and taking into account age, extent of early changes of AMD, smoking history, body mass index and educational status (7). A subset of the genetic test results are intended for use to identify patients who would benefit from treatment with a combination of high dose vitamins and minerals (8).

An alternative genetic test for AMD is being marketed by Sequenom CMM. Their RetnaGene test uses 13 genetic variants in the major AMD associated genes (including rs2230199 in C3) to predict the risk of choroidal neovascularisation, based on a study by Hageman et al (9). The importance of including rs2230199 in genetic tests for AMD has led to Sequenom mounting a legal challenge to the Cambridge patent (2).

5. Sources to corroborate the impact (indicative maximum of 10 references)

(1) Zanke B, Hawken S, Carter R, Chow D. A genetic approach to stratification of risk for age-related macular degeneration. Can J Ophthalmol. 2010;45:22-7. doi: 10.3129/i09-209.
(2) US Provisional Application No. 61/037,411 filed 18 March 2008; US Patent No. 8,114,592 filed 18 March 2009 and issued 12 February 2012. (Subsequently subject to legal challenge (Patent Interference No 105,897) resulting in a judgement by the US Patent and Trademark Office on 16 August 2013 that the discovery is unpatentable).
(3) http://www.arcticdx.com/genetics-of-amd/why-get-tested-
(4) Yu Y, Reynolds R, Rosner B, Daly MJ, Seddon JM. Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov models. Invest Ophthalmol Vis Sci. 2012;53:1548-56. doi:10.1167/iovs.11-8657.
(5) Personal communication from, Chief Medical Officer of ArcticAx.
(6) http://www.dailymail.co.uk/health/article-1038572/New-test-identify-vulnerable-AMD--UKs-common-form-blindness.html#axzz2KarQoxFj
(7) http://www.macularisk.com/home/
(8) http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=2&cad=rja&ved=0CDMQFjAB&url=http%3A%2F%2Fwww.hsc.nihr.ac.uk%2Ffiles%2Fdownloads%2F2168%2F2474.9f47aa3c.FinalArcticDxMacularRiskPGx.pdf&ei=enVeUp_jFqGK0AWFjoDoBg&usg=AFQjCNH2Tgy5dxC7pdud2STiZIxtbvvaKA
(9) Hageman GS, Gehrs K, Lejnine S, et al. Clinical validation of a genetic model to estimate the risk of developing choroidal neovascular age-related macular degeneration. Hum Genomics. 2011;5:420-40.