Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Molecular genetic characterisation of the causes of familial hypercholesterolaemia has led to improved diagnosis, prevention and treatment.

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

Basic molecular genetic research undertaken over the last 20 years by UCL Cardiovascular Genetics has had a significant impact on the identification and treatment of patients with familial hypercholesterolaemia (FH). We have developed DNA testing methods in the three genes currently known to cause FH and have established DNA diagnostic protocols which are now in wide use throughout the UK. As a direct consequence of our work, we estimate that up to 3,000 FH patients in the UK have had their diagnosis of FH confirmed by a DNA test. Our work led to the National Institute of Health and Clinical Excellence (NICE) in 2008 strongly recommending DNA and cascade testing and early treatment with high intensity statins, and furthermore, the inclusion of FH checks in the NHS's Vascular Checks programme.

2. Underpinning research (indicative maximum 500 words)

The impacts reported below are the result of basic molecular genetic research undertaken over the last 20 years that have had a significant impact on the identification and treatment of patients with familial hypercholesterolaemia (FH). This work led to the establishment of a DNA diagnostic service at the Great Ormond Street Hospital in 1997 and the establishment of the UCL LDLR mutation database, curated by the UCL Cardiovascular Genetics Group, which is regularly updated **[1]**.

We initially developed high-throughput screening methods – necessary because FH is so common – which have been adapted for use in the DNA diagnostic laboratory setting. Until recently, detecting all possible mutations that predispose a patient to FH would be expensive, labour intensive, and difficult to implement in clinical practice. We developed a kit which, by examining 20 different mutations would rapidly and cheaply identify the defect in roughly 50% of all patients where a mutation could be identified by a complete gene screen **[2]**. We further reported that c.5% of patients with FH have a large deletion/rearrangement of the LDLR gene and proposed a diagnostic algorithm that tests for the 20 most common mutations, followed by sequencing of LDLR in those with no detected mutation and finally using a commercially available MLPA kit to screen for deletions or rearrangements **[2]**. Using these approaches, mutations can be found in up to 80% of FH patients with the strongest clinical diagnosis, but in those were no mutation can be detected we recently demonstrated that a polygenic (not a single gene) cause is most likely **[3]**.

In 2000 we reported on the under-diagnosis of FH patients in the Oxfordshire area, particularly in young adults (who would benefit most from statin treatment) and confirmed this in a UK national survey. Together with colleagues at the LSHTM, we then carried out a modelling exercise to determine the efficacy of cascade testing vs. other screening approaches, and showed that cascade testing was likely to be the most cost effective method and was within NICE costing requirements **[4]**.

Our work in 2006-9 demonstrated the feasibility and acceptability of cascade testing through a pilot study, in a Department of Health-funded project involving five sites throughout the UK **[5]**. We also analysed the ethical issues involved and proposed appropriate ways of dealing with them. With colleagues at Kings College London we demonstrated that DNA testing was not associated with significantly greater levels of anxiety than measuring plasma cholesterol levels and that it was associated with a number of favourable effects **[6]**.

For patients where the causative mutation cannot be identified, we developed age and gender specific LDL cholesterol cut-offs that would allow a clear distinction between those with a high

probability of not having FH versus a high probability of definitely having FH. We defined the area of uncertainty where further testing and follow up will be required **[7]**.

In collaboration with Andrew Neil at the University of Oxford and the Simon Broome Register Group, we analysed data from the Simon Broome FH register (a computerised research register of FH patients, used to track the progression of the disease in the UK) to demonstrate a significant increase in life expectancy in treated FH patients, firstly with the initially available low potency statins, and subsequently with high potency statins which have become available in the last ten years. Although FH patients on the register who already have heart disease still have a roughly two-fold higher future risk of a fatal CHD event even if well treated, those who do not have evidence of heart disease can, when treated with high intensity statins, expect to have a life expectancy which is not significantly lower than the general population **[8]**.

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

[1] Usifo E, Leigh SE, Whittall RA, Lench N, Taylor A, Yeats C, Orengo CA, Martin AC, Celli J, Humphries SE. Low-density lipoprotein receptor gene familial hypercholesterolemia variant database: update and pathological assessment. Ann Hum Genet. 2012 Sep;76(5):387-401. http://dx.doi.org/10.1111/j.1469-1809.2012.00724.x

[2] Taylor A, Patel K, Tsedeke J, Humphries SE, Norbury G. Mutation screening in patients for familial hypercholesterolaemia (ADH). Clin Genet. 2010 Jan;77(1):97-9. http://doi.org/c9799x

[3] Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA, Harrison SC, Li K, Drenos F, Karpe F, Neil HA, Descamps OS, Langenberg C, Lench N, Kivimaki M, Whittaker J, Hingorani AD, Kumari M, Humphries SE. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet. 2013 Apr 13;381(9874):1293-301. http://doi.org/f2hmx4

[4] Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil AW. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. BMJ. 2002 Jun 1;324(7349):1303. http://dx.doi.org/10.1136/bmj.324.7349.1303

[5] Hadfield SG, Horara S, Starr BJ, Yazdgerdi S, Marks D, Bhatnagar D, Cramb R, Egan S, Everdell R, Ferns G, Jones A, Marenah CB, Marples J, Prinsloo P, Sneyd A, Stewart MF, Sandle L, Wang T, Watson MS, Humphries SE; Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade Testing Audit Project. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem. 2009 Jan;46(Pt 1):24-32. http://dx.doi.org/10.1258/acb.2008.008094

[6] Marteau T, Senior V, Humphries SE, Bobrow M, Cranston T, Crook MA, Day L, Fernandez M, Horne R, Iversen A, Jackson Z, Lynas J, Middleton-Price H, Savine R, Sikorski J, Watson M, Weinman J, Wierzbicki AS, Wray R. Genetic Risk Assessment for FH Trial Study Group. Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. Am J Med Genet A. 2004 Jul 30;128A(3):285-93. http://dx.doi.org/10.1002/ajmg.a.30102

[7] Starr B, Hadfield SG, Hutten BA, Lansberg PJ, Leren TP, Damgaard D, Neil HA, Humphries SE. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clin Chem Lab Med. 2008;46(6):791-803. http://doi.org/c3hpq4

[8] Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, Seed M, Humphries SE. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J. 2008 Nov;29(21):2625-33. http://dx.doi.org/10.1093/eurheartj/ehn422

Peer-reviewed funding

Over the period 1993-2013, Humphries received peer-reviewed research funding from the British Heart Foundation of > £6.6m, of which 25-30% is dedicated to FH work (ie £1.6-2.0 million). He received three grants from the Department of Health, for the London Genetic Knowledge Park of £3.4m of which 10% was for FH, of £1.2m for the Cascade-Audit FH project (100% FH) and for communication risk of £158,000 (50% FH). He received two FH grants from the UCL Biomedical Research Centre, in total £185,000, a CASE studentship from the MRC of £84,000, and peer-reviewed funding from two small charities, in total £188,000.

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

The underpinning research described above has had a major impact in transforming the management and identification of patients with FH. The three specific impacts described below are: (1) development and validation of screening methods which are now in use throughout the UK; (2) contribution of research to the development of NICE guidelines (CG71); (3) impact on the design of the NHS's Vascular Checks programme to increase the reach of our work.

FH is one of the most common Mendelian disorders, affecting 1 in 500 members of the general population – or approximately 120,000 people in the UK. People with FH have very high levels of low density lipoprotein cholesterol (LDL-C) from birth and are at extremely high risk of developing early heart disease. This can be prevented by early treatment with a high intensity lipid-lowering therapy such as statins. Unfortunately, only 15,000 FH patients have been identified to date and are being adequately treated. Since FH is a monogenic disorder, the best way to find new FH patients is by identifying the genetic mutation in the proband and "cascade testing" all their first degree relatives, 50% of whom will also be carriers.

DNA screening methods we developed have been used commonly in DNA diagnostic laboratories throughout the UK. The identification and characterisation of the common mutations in LDLR, APOB and PCSK9 in FH patients in the UK led to the development of a DNA test kit which was commercialised by Tepnel (now Geneprobe) during the Department of Health-funded London IDEAS Genetic Knowledge Park of which Professor Humphries was CEO. Although now superseded by new technologies, the availability of the Elucigene FH20 kit allowed labs to take on FH genetic testing and offer it widely and therefore led to the identification of the molecular cause of FH in a large number of patients. This information was then used for testing their relatives. In 2008, Humphries also contributed to the first UK Genetic Testing Network "Gene Dossier" for FH obtained by the GOSH DNA laboratory **[a]**.

The demonstration of the feasibility, acceptability and cost-effectiveness of FH cascade testing carried out at UCL was a major part of the evidence that was presented to the NICE Guideline Development Group, which led to their recommendation that DNA testing should be offered to all FH patients to confirm their diagnosis and to use the DNA information for cascade testing in their relatives **[b]**. The NICE guidelines (CG71) for the identification and management of FH patients were published in 2008 and Humphries was the Lead Clinical Advisor for these guidelines. Implementation guidelines and costing tools were also part of the NICE work, along with further NICE Quality Standards, published in August 2013.

Progress in implementing these guidelines was examined in a pilot audit, again led by Humphries and run through the Royal College of Physicians, which reported in 2009 **[c]**. This was followed by a national audit of 140 Lipid Clinics in the UK which reported in December 2010. The audit revealed that DNA and cascade testing had been implemented well in Scotland, Northern Ireland and Wales but almost not at all in England. Nevertheless, 26% of patients seen over a 5-month period at the surveyed clinics were offered a DNA test. At that time, only 21% of trusts reported that they had access to a family cascade testing system for FH, but where individuals had a DNA test, the process of cascade testing was initiated in 72% of adults and 54% of paediatric cases **[d]**. According to the Clinical Molecular Genetics Society Audit of Data for the year 2011-2012, a total of 3,235 DNA tests for FH were performed in the laboratories of its members (including all the

Regional Genetic Laboratories) during that period. The audit reported that this was an increase over previous years **[e]**. Humphries has continued public awareness work since the report was published, with articles about cascade testing appearing, for example, in the Daily Mail, on BBC News and in the Guardian **[f]**.

In order to identify further FH patients as index cases for cascade testing, Humphries has worked with the National Screening Committee to include FH criteria in the NHS Vascular Checks programme **[g]**. Individuals with a total cholesterol level over 7.5mmol/l who, based on the diagnostic criteria of the Simon Broome Register, are likely to have FH, will be flagged and referred to their local lipid clinic **[h]**.

Information on FH has been made available to all UK GPs through a 2009 BHF factfile prepared by Humphries **[i]**. Our research findings are outlined (and directly referenced) in the information given, and cascade screening is recommended. Information based on our research is also given to patients through articles in the HEARTUK magazine and their website **[j]**.

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

[a] UK Genetic Testing Network Gene Dossier for Familial Hypercholesterolaemia http://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/test-service/familial-hypercholesterolemia-218

[b] Clinical Guidelines (CG71) – Familial hypercholesterolaemia. http://www.nice.org.uk/nicemedia/pdf/CG071 (citing ref. 2 above, and other papers by the group)

[c] National Clinical Audit of the Management of Familial Hypercholesterolaemia 2009: Pilot FULL REPORT June 2009 http://www.rcplondon.ac.uk/sites/default/files/fh-pilot-audit-2009-report.pdf

[d] Pedersen KMV, Humphries SE, Roughton M, Besford JS. National Clinical Audit of the Management of Familial Hypercholesterolaemia 2010: Full Report. Clinical Standards Department, Royal College of Physicians, December 2010 http://www.rcplondon.ac.uk/resources/audits/FH

[e] Clinical Molecular Genetics Society Audit of Data for years 2011-2012: http://www.cmgs.org/CMGS%20audit/2012%20audit/CMGSAudit11_12_FINAL.pdf (Number of tests, see p.11; increase in tests, see p.12

[f] Media articles:
- Article in the Daily Mail: http://www.dailymail.co.uk/health/article-2151319/Have-YOU-inherited-heart-attack-gene-He-healthy-eater-Jonathan-needed-needed-triple-heart-bypass.html
- BBC News item: http://www.bbc.co.uk/news/health-12266621
- Guardian article: http://www.guardian.co.uk/society/2013/jan/22/blood-screening-heart-attacks

[g] Advising the Nation Screening Committee FH Policy Review 2011 http://www.screening.nhs.uk/familialhypercholesterolaemia-adult

[h] NHS Health Check: Vascular Risk Assessment and Management Best Practice Guidance. http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_097489

[i] British Heart Foundation Fact File on FH published 2009 http://www.bhf.org.uk/publications/view-publication.aspx?ps=1000885

[j] HEARTUK web site on FH. http://www.heartuk.org.uk/images/uploads/beendiagnosedpdfs/fhbooklet.pdf
Further confirmation of the contribution of the underpinning research to the development of cascade testing is available from the Chief Executive of HEARTUK. Contact details provided.