Institution: Queen Mary University of London (QMUL)

Unit of Assessment: A5 (Biological Sciences)

Title of case study: CS3 – Body odour disorder Trimethylaminuria has a genetic origin and is not due to poor hygiene

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

Our research has established that Trimethylaminuria (TMAU) – a rare and distressing disorder where affected individuals excrete large amounts of odorous trimethylamine (TMA) in their breath, sweat and urine – is a genetic disorder, and is not, as previously thought, due to poor hygiene. This has transformed understanding in the medical community and the wider public of why some people have an extremely unpleasant 'fishy' body odour, and has been crucial to helping individuals with TMAU who often suffer social isolation, rejection, depression and higher than normal suicide rates. The findings have led to genetic diagnosis and genetic counselling for TMAU in the UK, Europe, USA and Canada and the publication of guidelines for the diagnosis and treatment of the disorder.

2. Underpinning research (indicative maximum 500 words)

The impacts reported here stem from basic molecular biology, biochemistry and molecular genetic research undertaken from the 1993 to 2003. It was known that TMA could be converted to its N-oxide by a flavin-containing monooxygenase (FMO) in the liver and that individuals responded differently to a trimethylamine challenge. Thus a genetic origin for TMAU was suspected. This research took place without the benefit of the rapid sequencing and genome resources available today. A systematic cDNA cloning strategy identified five distinct FMO mRNAs and the five corresponding genes were mapped to the long arm of human chromosome 1 [a, b]. Analysis of expression patterns in human tissue [c] identified FMO3 as the best candidate for the disorder. Using a-then-novel method, the structural organization of the FMO3 gene was determined directly from genomic DNA [d]. Amplification and DNA sequencing of exons identified a mutation in an affected individual that changed pro153 to leu153. The child was homozygous for the mutation and the parents were heterozygous for this mutation. The mutant protein was expressed from its cDNA and shown to be unable to convert TMA to TMA N-oxide. These results led, in 1997, to a paper in Nature Genetics reporting for the first time a genetic basis for TMAU [e].

This was accompanied by media coverage across the globe, which began the process of an understanding of the genetic contribution to TMAU. We and others subsequently identified additional mutations in the FMO3 gene that cause TMAU in different families. Some cases proved to be caused by compound heterozygosity [f]. In 2003 we created a database of FMO3 mutations to inform researchers, patients and medical practitioners [g]. All the impacts described here were dependent on work carried out by Phillips as a lead researcher at Queen Mary University of London and were carried out in collaboration, and supported by joint grants, with E A Shephard at University College London and initially also with R. L. Smith at St Mary's Hospital Medical School.

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

a) Shephard EA, Dolphin CT, Fox MF, Povey S, Smith R, Phillips IR, Localization of genes encoding three distinct flavin-containing monooxygenases to human chromosome 1q. (1993) *Genomics* 16: 85-89.
b) Phillips IR, Dolphin CT, Clair P, Hadley MR, Hutt AJ, McCombie RR, Smith RL, Shephard EA, The molecular biology of the flavin-containing monooxygenases of man. (1995) *Chem Biol Interact* 96:17-32.
c) Dolphin CT, Cullingford TE, Shephard EA, Smith RL, Phillips IR, Differential developmental and tissue-specific regulation of expression of the genes encoding three members of the flavin-containing monooxygenase family of man, FMO1, FMO3 and FM04. (1996) *Eur J Biochem* 235: 683-689.

d) Dolphin CT, Riley JH, Smith RL, Shephard EA, Phillips IR, Structural organization of the human flavin-containing monooxygenase 3 gene (FMO3), the favored candidate for fish-odor syndrome, determined directly from genomic DNA. (1997) *Genomics* 46: 260-267.
e) Dolphin CT, Janmohamed A, Smith RL, Shephard EA, Phillips IR, Missense mutation in flavin-containing mono-oxygenase 3 gene, FMO3, underlies fish-odour syndrome. (1997) *Nat Genet* 17: 491-494.
f) Dolphin CT, Janmohamed A, Smith RL, Shephard EA, Phillips IR, Compound heterozygosity for missense mutations in the flavin-containing monooxygenase 3 (FM03) gene in patients with fish-odour syndrome. (2000) *Pharmacogenetics* 10: 799-807.
g) Hernandez D, Addou S, Lee D, Orengo C, Shephard EA, Phillips IR, Trimethylaminuria and a Human FMO3 Mutation Database. (2003) *Hum. Mutat.* 22: 201-213.

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

The impact of our work on TMAU has led to a global understanding by the medical profession of the genetic basis of the disorder of body odour. Our research has also positively impacted on TMAU sufferers, through the establishment of patient support groups and, in 2010, the creation of MEBO, a patient advocacy group for those that suffer from body odour disorders [1, 2].

In 2007, at the invitation of the National Institutes of Health (NIH), we produced a TMAU resource for the medical profession, patients and the public [3], which was updated in 2011. The resource provides information on the disorder, its diagnosis and its treatment. In 2012, at the invitation of EuroGentest, an EU Network of Excellence, we published European guidelines (Clinical Utility Gene Card) for genetic testing of TMAU [4]. Genetic testing for TMAU is now available through the NHS (Sheffield Children's NHS Foundation Trust, Sheffield Diagnostic Genetics Service) and in the USA, Canada and Europe through diagnostic laboratories. To communicate to the patients and medical profession the numerous mutations that can cause TMAU we created, in 2003, a database of FMO3 mutations [5]. The database, which is curated at UCL and, since January 2013, has been hosted at LOVD, permits researchers to submit new mutations and thus increases the resource for genetic testing services and patients who elect for testing. TMAU is now being included in medical education programmes, both in the US and UK, and the disorder is described in the student textbook 'Cell Biology, A Short Course' (2011).

The unusual nature of TMAU has led to close links between researchers and patients. Our research into FMOs and the cause of TMAU was funded by the Wellcome Trust and in 1999 the Trust co-hosted, with the NIH, a meeting in the US to which leading researchers in FMOs and individuals with TMAU and their families were invited. Phillips was a member of the international planning and advisory committee, and the impact of this meeting was to produce interactions among patient groups, and between researchers and patients which continue today. He has also assisted the National Organisation for Rare Disorders (NORD) and the Genetic and Rare Diseases Information Center (GARD), both offices of the NIH, with their articles and websites on TMAU [6,7]. In 2011 he also took part in a TMAU webinar hosted on the Rare Connect website, a partnership between EURODIS and NORD, which aims to connect patients suffering from rare conditions [8].

The patient advocacy group 'MEBO' has a global reach providing support and advice to those who suffer from TMAU. It has registered branches in the USA, UK and elsewhere in Europe [1, 2]. The organization now raises funds for further research into TMAU treatment and in 2011 raised sufficient funds for the NIH National Organization for Rare Disorders (NORD) to call for expressions of interest in TMAU research. Phillips has been a scientific advisor to group since 2011. A spokesperson for MEBO said "Professor Ian Phillips provides significant scientific guidance to MEBO and assists MEBO with advice when its initiates body odour testing programs ….. The NIH info co-authored by Professor Ian Phillips is repeatedly recommended to TMAU patients in all of the MEBO online sites, including websites, blogs, forums, Facebook site, and Skype site" [1, 3].

Urine and genetic testing for TMAU are now available on the NHS – this is not the case in most countries, where patients must pay for costly tests. With the advent of cheaper DNA sequencing

MEBO is assisting patients who elect to have their FMO3 gene sequenced. Phillips assists with interpretation of the sequencing reads and explanation of the results to patients. He is collaborating with a member of MEBO to produce a short primer on how to understand the sequencing output, which will be posted on the MEBO site [1, 2].

TMAU affects all ethnic groups and the disorder has been the subject of several TV programmes (e.g., Channel 4 'Embarrassing Bodies' – 2011), radio and the press [9]. This coverage has had a significant impact in promoting public understanding of the condition. In 2007 TMAU was included in the book entitled *When a gene makes you smell like a fish: and other tales about the genes in your body* published by Oxford University Press and reviewed in national newspapers including the *Guardian*.

Although TMAU is not a life-threatening disorder, it does make life very difficult for sufferers, with many experiencing social isolation and depression. The patient advocacy group MEBO said: "Prior to Professor Ian Phillips' research establishing TMAU as a genetic disorder, most sufferers were confused by their conditions and struggled on uncomprehending for years …..TMAU sufferers were frequently ostracised by society, and sometimes rebuffed by the medical profession …..Professor Ian Phillips' research changed that. Malodour sufferers now know that they are suffering from a recognised medical condition" [1, 9].

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

1. UK Public Relations Director for MEBO Research: The Directors of MEBO have provided a statement detailing Phillips' involvement with the TMAU patient advocacy group and the positive impact Phillips' work has had on TMAU sufferers

2. Website for the patient advocacy group MEBO: www.meboresearch.org/trimethylaminuria.html

3. NIH online TMAU resource for medical professionals, patients and the public: Phillips IR Shephard EA, (2007) and (2011) Trimethylaminuria. In: GeneReviews at GeneTests: Medical Genetics Information Resource. Copyright, University of Washington, Seattle. www.ncbi.nlm.nih.gov/books/NBK1103/

4. European guidelines for genetic testing of TMAU: Shephard EA, Treacy E, Phillips IR (2012) Clinical utility gene card for: Trimethylaminuria. Eur J Hum Genet, 20. doi:10.1038/ejhg.2011.214

5. The FMO3 database, which has been updated and is now hosted on the Leiden Open Variation Database (LOVD) – http://databases.lovd.nl/shared/genes/FMO3 (the original FMO3 database – hosted at http://www.hgvs.org/dblist/glsdb.htm#F is no longer available)

6. Website/report article for National Organisation for Rare Disorders (NORD), co-authored by Phillips, regarding TMAU: www.rarediseases.org/rare-disease-information/rare-diseases/byID/997/viewAbstract

7. Website/report article for the Genetic and Rare Diseases Information Center (GARD): www.rarediseases.info.nih.gov/GARD/Condition/6447/Trimethylaminuria.aspx

8. EURODIS and NORD webinar on TMAU presented by Prof. Shephard and Prof. Phillips: www.rareconnect.org/en/community/trimethylaminuria/article/2nd-tmau-webinar also available here: www.bloodbornebodyodorandhalitosis.com/2012/09/tmaufmo3-webinar-recording-professors.html

9. Example of the media coverage surrounding TMAU and one sufferer's story of how the

discovery of a genetic basis for this disease made him feel relieved that his body odour was a result of a medical problem and due to not poor hygiene: www.theworld.org/2012/03/tmau-genes