Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Elucidating the genetics of deafness leads to better diagnosis and clinical services

1. Summary of the impact

Our research has had impact on the activities of practitioners and their services, health and welfare of patients, on society and on public policy. New **diagnostic tests** for genetic deafness have been introduced, and **healthcare guidelines and professional standards** adopted through our investigation of the aetiology of childhood-onset hearing loss. Disease prevention has been achieved by our research on antibiotic-associated deafness, **public awareness of risk to health** and hearing has been raised, and we have **increased public engagement** through debate on scientific and social issues. We have also influenced **public policy on ethics of genetic testing** for deafness with our research resulting in **improved quality, accessibility and acceptability of genetic services among many hard-to-reach groups** (deafblind, culturally Deaf, and the Bangladeshi population of East London).

2. Underpinning research

Since 1993, the UCL Institute of Child Health has conducted a research programme into the genetics of deafness, initially under the leadership of Professor Marcus Pembrey, Mothercare Professor of Clinical Genetics and Fetal Medicine, and subsequently under Professor Maria Bitner-Glindzicz, Professor of Clinical and Molecular Genetics. We have identified genes causing both syndromic and non-syndromic forms of deafness through the detailed study of families presenting to audiology and genetics departments at Great Ormond Street Hospital and recently to UCLP hospitals.

In 1995, together with a group from the Department of Human Genetics, University Hospital Nijmegen, we identified *POU3F4*, the first gene for non-syndromic deafness in humans **[1]**. The programme continued with discovery of genes for Branchio-oto-renal syndrome **[2]**, Cardio-Auditory Syndrome **[3]** and Usher syndrome **[4]** (deafness and progressive retinal degeneration) in 2000. We continued this work by examining functional effects of mutations in ion channel genes in an effort to understand why some mutations cause disease in the homozygous or heterozygous state **[5]**.

As well as laboratory-based studies we have also engaged in clinical research and genetic epidemiological studies. We contributed to a multi-centre study (led by Van Camp, University of Antwerp) **[6]** in which we studied the relationship between genotype and phenotype in *GJB2*, the commonest form of genetic deafness worldwide. This produced evidence of significant correlations, information that is used on a daily basis in genetic counselling clinics.

Our discovery of the *USH1C* gene in one form of Usher syndrome led to one of the largest clinical and molecular cohort studies worldwide, improved and established diagnostic services for patients (including prenatal diagnosis). This finding established a specialised clinic for dual sensory impairment, and engaged this hard-to-reach group with multisensory impairment in ongoing research. Exhaustive genetic analysis has refuted digenic inheritance as an important contribution to this disease **[7]**. Clinical studies have documented visual acuity and field loss with age, prognostic information that is now used in counselling situations.

Our work on an environmental cause of deafness, antibiotic-associated deafness, published in NEJM **[8]**, has strengthened the case for genetic testing prior to aminoglycoside administration. This resulted in changes in clinical practice in situations where patients are likely to have prolonged exposure. It has attracted media attention and public interest and engagement of patient groups in further research. In addition it has catalysed links with industry for the development of bedside

genetic testing.

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

[1] de Kok YJ, van der Maarel SM, Bitner-Glindzicz M, et al. Association between X-linked mixed deafness and mutations in the POU domain gene POU3F4. Science. 1995 Feb 3;267(5198):685-8. http://dx.doi.org/10.1093/hmg/4.8.1467

[2] Abdelhak S, Kalatzis V, Heilig R, et al. A human homologue of the Drosophila eyes absent gene underlies branchio-oto-renal (BOR) syndrome and identifies a novel gene family. Nat Genet. 1997 Feb;15(2):157-64. http://dx.doi.org/10.1038/ng0297-157

[3] Tyson J, Tranebjaerg L, Bellman S, Wren C, Taylor JF, Bathen J, Aslaksen B, Sørland SJ, Lund O, Malcolm S, Pembrey M, Bhattacharya S, Bitner-Glindzicz M. IsK and KvLQT1: mutation in either of the two subunits of the slow component of the delayed rectifier potassium channel can cause Jervell and Lange-Nielsen syndrome. Hum Mol Genet. 1997 Nov;6(12):2179-85. http://dx.doi.org/10.1093/hmg/6.12.2179

[4] Bitner-Glindzicz M, Lindley KJ, Rutland P, et al. A recessive contiguous gene deletion causing infantile hyperinsulinism, enteropathy and deafness identifies the Usher type 1C gene. Nat Genet. 2000 Sep;26(1):56-60. http://dx.doi.org/10.1038/79178

[5] Huang L, Bitner-Glindzicz M, Tranebjaerg L, Tinker A. A spectrum of functional effects for disease causing mutations in the Jervell and Lange-Nielsen syndrome. Cardiovasc Res. 2001 Sep;51(4):670-80. http://dx.doi.org/10.1016/S0008-6363(01)00350-9

[6] Snoeckx RL, Huygen PL, Feldmann D, et al. GJB2 mutations and degree of hearing loss: a multicenter study. Am J Hum Genet. 2005 Dec;77(6):945-57. http://doi.org/ch6rrf

[7] Le Quesne Stabej P, Saihan Z, Rangesh N, Steele-Stallard HB, Ambrose J, Coffey A, Emmerson J, Haralambous E, Hughes Y, Steel KP, Luxon LM, Webster AR, Bitner-Glindzicz M. Comprehensive sequence analysis of nine Usher syndrome genes in the UK National Collaborative Usher Study. J Med Genet. 2012 Jan;49(1):27-36. http://doi.org/cb95tr

[8] Bitner-Glindzicz M, Pembrey M, Duncan A, et al. Prevalence of mitochondrial 1555A-->G mutation in European children. N Engl J Med. 2009 Feb 5;360(6):640-2. http://dx.doi.org/10.1056/NEJMc0806396

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

Genetic tests introduced into clinical practice. Our research discoveries have been translated into diagnostic tests for patients which are in routine use in the NHS. For example, in the year ending 2011, our NHS Genetics laboratory performed diagnostic tests for genetic deafness disorders in over 1,100 UK patients, and we provided both molecular and clinical input to reports. Nationally, in the same year, 1,803 tests for GJB2 were carried out, according to an audit by the Clinical Molecular Genetics Society (CMGS) **[a]**. In 2012, a further gene dossier was approved by the UKGTN (UK Genetic Testing Network) for POU3F4 (X-linked deafness) **[b]**. We also obtained funding to establish massive parallel sequencing to underpin diagnosis in non-syndromic hearing loss and Usher syndrome, increasing the number of genes screened by almost tenfold. We expect this to improve the diagnostic yield by almost 100%, based on preliminary results and the work of others. The benefit to patients of this work is to clarify the inheritance and allow personalised genetic counselling.

Establishment of genetic deafness clinics. We established the first dedicated genetic deafness clinic in the UK and the only multidisciplinary dual sensory impairment clinic **[c]**. We see over 300 patients per year in these clinics for diagnosis and genetic counselling. One patient group we have worked with explained the impacts of this clinic on patients with Usher Syndrome as follows:

"By attending the clinic, and sometimes engaging in the genetic research programmes, people with Usher have been seen by us to benefit by:

- *Gaining full and reliable knowledge about Usher, and more especially which type of Usher they have…*
- *Gaining an understanding of the genetics of the condition. Some individuals have wrongly apportioned 'blame' for their condition since they did not understand the genetics involved. Others use the information to work with family and siblings who may also have Usher. Most importantly the support allows people to make an informed decision about having their own families in future, or about having further children following a diagnosis in an existing child.*
- *Allowing planning for the future when understanding the Usher type and its possible prognosis. Decisions need to be made on support, communication, mobility and access to information.*
- *Learning about or taking part in the research into Usher allows individuals to think about the future and may result in positive feelings for the future.*
- *Mental health impact – people have indicated to us that they are relieved to learn more about their condition, to accept Usher and to move forward with a firm diagnosis and understanding.*
- *Assisting families in their understanding of the condition, what the implications are and that they are not to 'blame'"* **[d]**.

Prenatal diagnosis. Human Fertilisation and Embryology Authority (HFEA) licences for Pre-implantation Genetic Diagnosis have been granted for two deafness conditions as a result of genes identified by our research **[e]**. This test is now in use in a number of centres as a result, allowing genetic counselling to take place.

Best Practice Guidelines. Our research has contributed to, and has been quoted by best practice clinical guidelines issued by the British Association of Audiovestibular Physicians (BAAP) **[f]**. Bitner-Glindzicz was a member of the working groups for three sets of guidelines: firstly, on *Aetiological investigation into severe to profound permanent hearing loss in children*, published in 2009, citing our work on Jervell and Lange-Nielsen Syndrome; secondly on *Aetiological Investigations into bilateral mild to moderate permanent hearing loss in children*, published in 2009, citing our work recommending blood tests for Connexin 26 mutations; thirdly on *Medical Evaluation of children with permanent unilateral hearing loss.* Our work is also cited in the BAAP's best practice guidelines on *Investigating infants with congenital hearing loss identified through the newborn hearing screening*. In 2013, Bitner-Glindzicz contributed to the European Molecular Genetics Quality Network (EMQN) *Best Practice guidelines for diagnostic testing of mutations causing non-syndromic hearing impairment at the DFNB1 locus* **[g]**.

Government Policy We advised the Department of Health Bill Team on amendments to Clause 14(4) of the Human Fertilization and Embryology Bill regarding embryo selection, particularly as it applied to deafness and the culturally Deaf community. Consequently the clause was re-worded to take account of the views of the Deaf Community **[h]**. We contributed to NIHR National Horizon Scanning Centre document on 'Genetic tests for screening pre-lingual hearing loss in newborns' for the National Institute for Health and Clinical Excellence (NICE) on the subject of potential advances in genetic technologies and their impact on screening newborns for deafness **[i]**. We were also invited to present our work to the All-Party Parliamentary Group in July 2012 at the House of Commons on the subject of Consent for Consent.

Media and Public Engagement Our work on causes and prevalence of deafness among Bangladeshi children in East London was featured on BBC local radio. Our research findings on antibiotic-associated deafness were featured in the Independent, the Daily Telegraph and on the BBC website, raising public awareness of this potentially-preventable cause of hearing loss **[j]**. We have engaged the public and parent groups in this research and two patient groups are represented on the Steering Committee of one of our current programmes of research. Throughout our programme of research we have been involved in public debate with the culturally Deaf

community regarding ethical issues; we have successfully engaged hard-to-reach groups in our research through Information Days and disseminated the subsequent findings through electronic media with the help of support groups such as deafblind charity Sense, who report that they "*highly value the impact we believe Professor Bitner-Glindzicz's work has had on the Usher population in the UK and would very keenly wish this to continue*" **[d]**.

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

[a] CGMS audit: http://www.cmgs.org/CMGS%20audit/2012%20audit/CMGSAudit11_12_FINAL.pdf

[b] NE Thames Regional Genetics Service Annual Report page 19: http://www.labs.gosh.nhs.uk/media/525571/ne_thames_rgs_annual_report_2011_2012.pdf

[c] http://www.gosh.nhs.uk/medical-conditions/clinical-specialties/clinical-genetics-information-for-parents-and-visitors/clinics/

[d] Letter of testimony from Information and Outreach Officer of the Sense Usher Specialist Service. Copy available on request.

[e] http://www.hfea.gov.uk/cps/hfea/gen/pgd-screening.htm Tests are for (a) Sensorineural deafness - autosomal recessive non-syndromic and (b) Branchio-Oto-Renal Syndrome (BOR)

[f] http://www.baap.org.uk/index.php?option=com_content&view=article&id=48&Itemid=54

[g] Hoefsloot LH, Roux AF, Bitner-Glindzicz M. EMQN Best Practice guidelines for diagnostic testing of mutations causing non-syndromic hearing impairment at the DFNB1 locus. Eur J Hum Genet. 2013 May 22 http://dx.doi.org/10.1038/ejhg.2013.83

[h] Clause 14(4) of Human Fertilization and Embryology Bill. DH Meeting Notes and Letter available on request.
See also, media discussion of the debate: http://www.bionews.org.uk/page_13332.asp

[i] 'Genetic tests for screening pre-lingual hearing loss in newborns' for the National Institute for Health and Clinical Excellence (NICE) NIHR Horizon Scanning: http://www.hsc.nihr.ac.uk/outputs/other-reports see p.20 of annual report 2011. Published as: Linden Phillips L, Bitner-Glindzicz M, Lench N, Steel KP, Langford C, Dawson SJ, Davis A, Simpson S, Packer C. The future role of genetic screening to detect newborns at risk of childhood-onset hearing loss. Int J Audiol. 2013 Feb;52(2):124-33. http://doi.org/nwj

[j] Examples of media and public engagement work:

- http://news.bbc.co.uk/1/hi/health/7866749.stm
- http://www.telegraph.co.uk/health/healthnews/4513095/Screen-mothers-for-gene-fault-that-could-lead-to-child-deafness-doctors-urge.html
- Independent article 'Antibiotics blamed for child deafness' http://www.independent.co.uk/life-style/health-and-families/health-news/antibiotics-blamed-for-child-deafness-1546400.html