Institution: University of Leeds

Unit of Assessment: UOA1 Clinical Medicine

Title of case study:
Case Study 8. Transforming the diagnosis and clinical management of autosomal recessive disease.

1. Summary of the impact

Congenital disorders are causes of major morbidity and mortality worldwide. Using autozygosity mapping in a local community of Pakistani origin who have high rates of inherited recessive disorders due to consanguineous unions, we have identified more than 30 novel disease genes. Isolating these previously unknown molecular defects has enabled us to develop key diagnostic assays, subsequently provided by clinical laboratories globally. Our work has provided thousands of patients with a definitive diagnosis, removing the need for complex clinical testing. Those affected can be offered focused management and early therapeutic intervention as well as carrier and prenatal testing for themselves and family members. Our findings also provide new research opportunities for previously undefined diseases.

2. Underpinning research

Congenital disorders, while individually rare, are collectively very common. The EU estimates as many as 6% of the population are affected. Around 75% of these disorders affect children and 30% of such patients die before the age of five.

An increased prevalence of recessive disorders is a major local healthcare burden in our local Pakistani community but has afforded us a unique research opportunity. We use autozygosity mapping, a technique that enables the identification of the chromosomal region that harbours the disease-causing gene, as outlined by **RF Mueller** (Professor of Clinical Genetics, Leeds 1995-2002) and **DT Bishop** (Professor of Genetic Epidemiology, Leeds 1989-present) (1). Applying this approach to our local clinical resource, the Yorkshire Regional Genetics Service, has resulted in the identification of more than 30 novel disease genes, for wide-ranging disorders including deafness, microcephaly, ciliopathies such as Joubert syndrome and several metabolic conditions.

The techniques we have pioneered generate large and complex datasets which in isolation provide little understanding. In order to analyse these datasets, **Dr I Carr** (Senior Research Fellow, Leeds 1999-present) has developed key software packages, which are freely available from our website (http://autozygosity.org/).

All our research is embedded within the clinical community caring for patients with inherited disorders and at present led by **EG Sheridan** (Senior Lecturer in Clinical Genetics, Leeds 2006-present) and **DT Bonthron** (Professor of Molecular Medicine, Leeds 2000-present) who both hold honorary clinical contracts with the Yorkshire Regional Genetics Service. Of the 30 previously unidentified disease genes we have isolated to date, there are four key areas of particular note.

1995-2002 – Deafness

Mueller led research to identify mutations in the connexion 26 (Cx26) gene as the commonest genetic cause of deafness, and clarified the role of Cx26 in a range of different types of deafness (2). We also developed guidelines for the establishment of genetic services for the deaf community [A].

1998-2005 – Microcephaly

AF Markham (Professor of Medicine, Leeds 1990-) and **CG Woods** (Senior Lecturer in Clinical Genetics, Leeds 1998-2005) carried out work on the genetic causes of the development of pathologically small brains. This included the identification of ASPM and MCPH1 as the commonest causes of the condition (3).

2001-present – Intracranial calcification

YJ Crow (Senior Lecturer in Clinical Genetics, Leeds 2001-2008) and **Bonthron** identified mutations in the TREX1 gene in patients with Aicardi-Goutieres syndrome - the first of three genes to be identified in this group of disorders (4).

2006-present – Abnormalities in renal tubular function

Sheridan was joint senior investigator in the detection of a fundamental protein involved in renal fluid handling in a study, which also defined a novel disorder; EAST syndrome. The *KCNJ10* gene was found to encode a potassium channel expressed in the brain, inner ear, and kidney, the existence of which had been postulated for 50 years prior to the work (5).

The 2006 report by the Chief Medical Officer raised the issue of unknown healthcare burden which results from disorders of this sort. Recent research by **Sheridan** has confirmed that consanguinity doubles the risk of congenital anomalies (6). This is an important global concern as more than one billion people live in societies with consanguinity rates >20%.

3. References to the research

1) Mueller RF, Bishop DT. Autozygosity mapping, complex consanguinity, and autosomal recessive disorders. J Med Genet 1993; 30: 798–99.
2) Lench N, Houseman M, Newton V, Van Camp G, and Mueller R. Connexin-26 mutations in sporadic non-syndromal sensorineural deafness. Lancet 1998; 351: 415.
3) Bond J, Roberts E, Mochida GH, Hampshire DJ, Scott S, Askham JM, Springell K, Mahadevan M, Crow YJ, Markham AF, et al. ASPM is a major determinant of cerebral cortical size. Nature Genetics 2002; 32: 316-20.
4) Crow YJ, Hayward BE, Parmar R, Robins P, Leitch A, Ali M, Black DN, van Bokhoven H, Brunner HG, Hamel BC, et al. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. Nature Genetics 2006; 38: 917-20.
5) Bockenhauer D, Feather S, Stanescu HC, Bandulik S, Zdebik AA, Reichold M, Tobin J, Lieberer E, Sterner C, Landoure G, Arora R, Sirimanna T, Thompson D, Cross JH, van't Hoff W, Al Masri O, Tullus K, Yeung S, Anikster Y, Klootwijk E, Hubank M, Dillon MJ, Heitzmann D, Arcos-Burgos M, Knepper MA, Dobbie A, Gahl WA, Warth R, Sheridan E, Kleta R. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. N Engl J Med 2009; 360: 1960-70.
6) Sheridan E, Wright J, Small N, Corry PC, Oddie S, Whibley C, Petherick ES,Malik T, Pawson N, McKinney PA, Parslow RC. Risk factors for congenital anomalyin a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet.2013 Jul 3. doi:pii: S0140-6736(13)61132-0. 10.1016/S0140-6736(13)61132-0.

4. Details of the impact

Our research has identified 30 genetic mutations associated with a range of inherited disorders and enabled us to develop definitive diagnostic tests which have subsequently been made available by laboratories around the world. Every novel molecular defect identified opens up new avenues of research for what can be previously undefined or little known conditions.

Impact on health and welfare

Many thousands of patients have now been tested for mutations in the disease genes we have identified. We sought to quantify this by contacting directly the labs offering tests.

In total 353 laboratories offering molecular genetics testing are listed on the Orphanet web site, which is primarily European, while the Genetests website lists over 600 such laboratories, with a greater emphasis on laboratories from the US and elsewhere (data confirmed 19/9/13). There is little overlap, with laboratories tending to list on one site or the other, and neither list is

comprehensive. It therefore seems likely that over 1000 laboratories around the world offer some form of genetic testing. Of these, 268 now offer a screen for *GJB2* (Connexin 26, ref 2). We contacted these and 15 responded, including 4 UK, 2 US and 9 European laboratories, stating that they carry out a total of around 1270 *GJB2* tests per year, with figures based largely on 2012 [A]. Recognising that this is a small sample, it does allow us to infer that perhaps in the order of 20,000 GJB2 screens may have been carried out in 2012 internationally, and our survey suggests that *GJB2* screening is increasing [A]. From the same sources above we identified 37 laboratories providing tests for the other genes noted.

A definitive diagnosis can be essential for patients who put a premium on knowing the cause of their condition. It can also have a substantial impact on their future care. More than a half of all patients with a genetic disease used to wait more than a year for a diagnosis, and are frequently given incorrect diagnoses [B]. The lack of an accurate test can mean fragmented care with different specialities and often unnecessary invasive clinical procedures [B]. Carrier and prenatal testing can hugely reduce the impact on families carrying a defective gene by allowing them to make informed reproductive choices [B]. A clear genetic diagnosis establishes the risks in future pregnancies and allows prenatal diagnosis. This is particularly important for disorders which are fatal

For many of the genetic conditions for which we have identified the cause, genetic diagnosis establishes the likely natural history and enables early intervention improve the outcome for the patient. Important examples include close surveillance for the seizure disorders, hearing loss and renal failure which are part of East syndrome (KCNJ10) [C]. Early identification of children with ASPM (microcephaly) mutations established the specific diagnosis in a syndrome with a wide range of different causes [D]. Deafness is one of the most common major abnormalities present at birth and a child with undetected hearing loss is at risk of failing to develop normal speech and language [E]. Presymptomatic identification of children with inherited hearing loss, only possible through genetic testing in high-risk families, permits the initiation of treatment, notably the fitting of hearing aids, at a very early age, significantly improving outcome [E].

The conditions for which we have identified a genetic cause are relatively rare. For example around 1 in 4000 individuals are affected by autosomal recessive deafness, primary microcephaly, Aicardi-Goutiere syndrome, and Joubert/Meckel syndromes. The burden of congenital disease in some populations and families is approximately doubled due to the practice of consanguineous marriage. Many characteristics of these conditions are mimicked by non–genetic conditions, so despite being rare, there are many patients for whom a test provides crucial information. For example 800 children are born every year in the UK with congenital hearing loss, about 25% of which is due to mutations in Cx26, but all warrant testing. Microcephaly is the presenting complaint of a wide variety of neurological disorders but all such cases should be tested for mutations in ASPM and MCPH1 as the commonest causes of primary microcephaly [D]. Aicardi-Goutiere syndrome can only be distinguished from congenital TORCH infection by genetic testing, obviating complex invasive clinical tests of doubtful value [F].

Impact on public policy and services

In recent years we have been at the forefront in the utilisation of Next Generation Sequencing (NGS) to identify disease-causing variants. Due to our close links with the Yorkshire Regional Genetics Service we have been able to facilitate the introduction of NGS into the NHS laboratory, this is the first NHS laboratory in which NGS analysis has been accredited for service provision [G].

It has always been a key goal of our work to make our research freely available. Around 20 years ago, efforts were made by US researchers to patent gene sequences to limit the widespread adoption of clinical testing. We were among the majority of UK and European researchers who rejected this policy in order to provide genetic testing to as many patients as possible. The software and data available on our website (http://dna.leeds.ac.uk/) is accessed by laboratories and researchers around the world. From our website there have been a total of 6809 downloads from unique IP addresses.

Impact on commerce

Around 300 laboratories across Europe, including the UK, are using the tests for the genetic abnormalities we have identified [A], with many thousands of patients offered a vital diagnosis and subsequent management for their condition, as outlined above. Diagnostic tests we identified are also provided in the US, and Australia.

The original discoveries we have made have been with the help of the local Pakistani heritage community – a group which has traditionally found it difficult to benefit fully from research projects which often fail to address their unique medical needs. We have provided genetic tests directly to families in Pakistan via their healthcare providers. We have provided clinical and academic training for genetic counselling staff in Pakistan [H].

5. Sources to corroborate the impact

[A] Collated information from genetic testing laboratories worldwide, detailing numbers of test carried out, significance and impact. Orphanet Portal. European reference portal for information on rare diseases and orphan drugs for all audiences. http://www.orpha.net/consor/cgi-bin/index.php?lng=EN

UK Genetic Testing Network (UKGTN). Body which advises the NHS on genetic testing. http://www.ukgtn.nhs.uk/gtn/Home

[B] Limb L, Nutt S, Sen A. UK RD. Experiences of Rare Diseases: An Insight From Patients and Families 2010. http://www.raredisease.org.uk/documents/RDUK-Family-Report.pdf

[C] Cross JH, Arora R, Heckemann RA, Gunny R, Chong K, Carr L, Baldeweg T, Differ AM, Lench N, Varadkar S, Sirimanna T, Wassmer E, Hulton SA, Ognjanovic M, Ramesh V, Feather S, Kleta R, Hammers A, Bockenhauer D. Neurological features of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome. Dev Med Child Neurol. 2013 Sep;55(9):846-56.

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[G] Clinical Pathology Accreditation for the Yorkshire Regional DNA Laboratory.

[H] Bryant LD, Ahmed S, Ahmed M, Jafri H, Raashid Y. 'All is done by Allah'. Understandings of Down syndrome and prenatal testing in Pakistan. Soc Sci Med. 2011 Apr;72(8):1393-9

[I] Letters of corroboration, confirming the impact of Leeds research on development of diagnostic tests for recessive diseases and consequent improvements for patients and families (Chair, British Society for Genetic Medicine; Assistant Professor of Pathology, Harvard Medical School; Director, Genetic Alliance UK)