Institution: The University of Manchester

Unit of Assessment: 1

Title of case study: The global impact of gene identification at the University of Manchester

1. Summary of the impact

Although, by definition, individually rare, the cumulative burden of 'rare disease' is significant, with as many as 3m affected individuals in the UK. The University of Manchester (UoM) has an exceptional record in rare disease gene identification, with 29 such genes defined since 1993. This research paved the way for clinical diagnostic testing for patients and their families, demonstrating the immediate translational impact of gene discovery. The research has resulted in a reduced diagnostic burden for patients and health services and has enabled the provision of more effective counselling. Testing for genes identified at UoM is now offered in more than 140 laboratories in more than 30 countries worldwide. More than 1,100 patients have been tested for mutations in *TCOF1*, *BEST1*, *IRF6*, *SAMHD1* and *C9ORF72* in UK NHS laboratories alone.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Research activity was carried out between 1993 and the present. The following researchers were all working at UoM at the time of the stated outputs:

- **Andrew Read** (Reader, 1992-1995; Professor, 1995-2004; Honorary Professor, 2004-date)
- **May Tassabehji** (Wellcome Senior Fellow, 1996-2007; Senior Research Fellow, 2007; Reader, 2007-date)
- **Mike Dixon** (Professor, 1996-date)
- **Graeme Black** (Lecturer, 1995-1997; Senior Lecturer, 1997-2003; Professor, 2003-date)
- **Jill Clayton-Smith** (Honorary Senior Lecturer, 1998-2006; Honorary Professor, 2006-date)
- **William Newman** (Research Training Fellow, 1997-2000; Clinical Senior Lecturer, 2004-date)
- **Yanick Crow** (Professor, 2008-date)
- **Nalin Thakkar** (Lecturer, 1992-1996; Senior Lecturer, 1996-2003; Professor, 2003-date)
- **Michael Briggs** (Postdoctoral Fellow, 1996-2000; Research Fellow, 2001-2005; Reader, 2005-2012)
- **Stuart Pickering-Brown** (Professor, 2005-date)

Outputs are only considered where:

1. At least one of the above UoM members of staff was the *Corresponding Author* (*Principal Investigator*) on the study;
2. Where the publication represents the first reporting of the disease gene, i.e. before the publication, the genetic basis of the study disease was unknown.

The discoveries linked to impact relate to the following genes and their associated phenotype (investigator and year of discovery in parenthesis):

1. *PAX3*: Waardenburg syndrome type 1 and 2 (**Read**, **Tassabehji**: 1993) **(1)**
2. *MITF*: Waardenburg syndrome (**Read**; **Tassabehji**: 1994)
3. *TCOF1*: Treacher Collins syndrome (**Dixon**: 1997)
4. *Cathepsin C*: Papillon-Lefèvre syndrome (**Thakkar**: 1999)
5. *ENAM*: Amelogenesis imperfecta (**Dixon**: 2001)
6. *Matrilin-3*: Multiple epiphyseal dysplasia (**Briggs**: 2001)
7. *MAF*: Congenital cataract, anterior segment dysgenesis and coloboma (**Black**: 2002)
8. *IRF6*: Van der Woude syndrome (**Dixon**: 2002) **(2)**
9. *BCOR*: Oculofaciocardiodental and Lenz syndromes (**Black**: 2004) **(3)**
10. *BEST1*: Autosomal recessive 'Bestrophinopathy' (**Black**: 2008)
11. *OBSL1*: 3M syndrome (**Black**: 2009)

12. *SAMHD1*: Aicardi-Goutières syndrome (**Crow**: 2009) **(4)**
13.*C2ORF71*: Retinitis pigmentosa (**Black**: 2010)
14. *HPSE2*: Urofacial syndrome (**Newman**: 2010)
15. *OCLN*: Band-like calcification with polymicrogyria (**Crow**: 2010)
16. *ACP5*: Spondyloenchondrodysplasia (**Crow**: 2011)
17. *DHFR*: Dihydrofolate reductase deficiency syndrome (**Newman**: 2011)
18. *FAM20A*: Amelogenesis imperfecta (**Dixon**: 2011)
19. *PRDM5*: Brittle cornea syndrome (**Black**: 2011)
20. *CCDC8*: 3M syndrome (**Black**: 2011)
21. *C9ORF72*: Motor neurone disease (**Pickering-Brown**: 2011) **(5)**
22. *KAT6B*: Ohdo syndrome (**Clayton-Smith**: 2011)
23. *RIPK4*: Bartsocas-Papas syndrome (**Dixon**: 2012)
24. *CTC1*: Coats plus syndrome (**Crow**: 2012)
25. *ADAR1*: Aicardi-Goutières syndrome (**Crow**: 2012) **(6)**
26. *CLPP*: Perrault syndrome (**Newman**: 2013)
27. *SMARCE1*: Multiple spinal meningioma (**Newman**: 2013)
28. *LRIG2*: Urofacial syndrome (**Newman**: 2013)
29. *PRKCD*: Systemic lupus erythematosus (**Crow**: 2013)

Disease genes were identified through a combination of patient recruitment, expert clinical selection and detailed phenotyping, allied to state-of-the-art genetic techniques including linkage analysis, homozygosity mapping, candidate gene sequencing and, most recently, next-generation technologies. The advent of new technologies has been mirrored by an increased rate of gene identification since 2010.

3. References to the research

The following six references are key examples from a much larger body of research produced at UoM since 1993:

1. **Tassabehji M, Read AP**, Newton VE, Patton M, Gruss P, Harris R, Strachan T. Mutations in the PAX3 gene causing Waardenburg syndrome type 1 and type 2. *Nature Genetics*. 1993;3(1):26-30. DOI: 10.1038/ng0193-26

2. Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, Howard E, Ferreira de Lima RLL, Daack-Hirsch S, Sander A, McDonald-McGinn DM, Zackai EH, Lammer EJ, Aylsworth AS, Ardinger HH, Lidral AC, Pober BR, Moreno L, Arcos-Burgos M, Valencia C, Houdayer C, Bahuau M, Moretti-Ferreira D, Richieri-Costa A, **Dixon MJ***, Murray JC. Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. *Nature Genetics*. 2002;32(2):285-9. DOI: 10.1038/ng985

3. Ng D, Thakker N, Corcoran CM, Donnai D, Perveen R, Schneider A, Hadley DW, Tifft C, Zhang L, Wilkie AOM, van der Smagt JJ, Gorlin RJ, Burgess SM, Bardwell VJ, **Black GCM*,** Biesecker LG. Oculofaciocardiodental and Lenz microphthalmia syndromes result from distinct classes of mutations in BCOR. *Nature Genetics*. 2004;36(4):411-6. DOI: 10.1038/ng1321

4. Rice GI, Bond J, Asipu A, Brunette RL, Manfield IW, Carr IM, Fuller JC, Jackson RM, Lamb T, Briggs TA, Ali M, Gornall H, Couthard LR, Aeby A, Attard-Montalto SP, Bertini E, Bodemer C, Brockmann K, Brueton LA, Corry PC, Desguerre I, Fazzi E, Cazorla AG, Gener B, Hamel BCJ, Heiberg A, Hunter M, van der Knaap MS, Kumar R, Lagae L, Landrieu PG, Lourenco CM, Marom D, McDermott MF, van der Merwe W, Orcesi S, Prendiville JS, Rasmussen M, Shalev SA, Soler DM, Shinawi M, Spiegel R, Tan TY, Vanderver A, Wakeling EL, Wassmer E, Whittaker E, Lebon P, Stetson DB, Bonthron DT, **Crow YJ**. Mutations involved in Aicardi-Goutieres syndrome implicate SAMHD1 as regulator of the innate immune response. *Nature Genetics*. 2009;41(7):829-32. DOI: 10.1038/ng.373

5. Renton Alan E, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick Jennifer C, Laaksovirta H, van Swieten John C, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes Anne M, Kaganovich A, Scholz Sonja W, Duckworth J, Ding J, Harmer Daniel W,

Hernandez Dena G, Johnson Janel O, Mok K, Ryten M, Trabzuni D, Guerreiro Rita J, Orrell Richard W, Neal J, Murray A, Pearson J, Jansen Iris E, Sondervan D, Seelaar H, Blake D, Young K, Halliwell N, Callister Janis B, Toulson G, Richardson A, Gerhard A, Snowden J, Mann D, Neary D, Nalls Michael A, Peuralinna T, Jansson L, Isoviita V-M, Kaivorinne A-L, Hölttä-Vuori M, Ikonen E, Sulkava R, Benatar M, Wuu J, Chiò A, Restagno G, Borghero G, Sabatelli M, Heckerman D, Rogaeva E, Zinman L, Rothstein Jeffrey D, Sendtner M, Drepper C, Eichler Evan E, Alkan C, Abdullaev Z, Pack Svetlana D, Dutra A, Pak E, Hardy J, Singleton A, Williams Nigel M, Heutink P, **Pickering-Brown S***, Morris Huw R, Tienari Pentti J, Traynor Bryan J. A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. *Neuron*. 2011;72(2):257-68. DOI: 10.1016/j.neuron.2011.09.010

6. Rice GI, Kasher PR, Forte GMA, Mannion NM, Greenwood SM, Szynkiewicz M, Dickerson JE, Bhaskar SS, Zampini M, Briggs TA, Jenkinson EM, Bacino CA, Battini R, Bertini E, Brogan PA, Brueton LA, Carpanelli M, De Laet C, de Lonlay P, del Toro M, Desguerre I, Fazzi E, Garcia-Cazorla A, Heiberg A, Kawaguchi M, Kumar R, Lin J-PSM, Lourenco CM, Male AM, Marques W, Mignot C, Olivieri I, Orcesi S, Prabhakar P, Rasmussen M, Robinson RA, Rozenberg F, Schmidt JL, Steindl K, Tan TY, van der Merwe WG, Vanderver A, Vassallo G, Wakeling EL, Wassmer E, Whittaker E, Livingston JH, Lebon P, Suzuki T, McLaughlin PJ, Keegan LP, O'Connell MA, Lovell SC, **Crow YJ**. Mutations in ADAR1 cause Aicardi-Goutieres syndrome associated with a type I interferon signature. *Nature Genetics*. 2012;44(11):1243-8. DOI: 10.1038/ng.2414
*Joint corresponding author

4. Details of the impact

See section 5 for corroborating sources S1-S9.

Context

While individually uncommon, rare diseases as a group represent a major public health issue. By definition each individual rare disease affects fewer than five in 10,000 people, but taken together they are common, with one in 17 people affected in the UK by a rare disease (S1, p. 7). Although there are many thousands of different rare diseases, they frequently share a number of characteristics. These include a severe, chronic, often degenerative and sometimes life-threatening course. Most rare diseases are incurable and lack effective treatment.

Pathways to impact

The identification of the genetic basis of a rare disease by UoM immediately allows for diagnostic/confirmatory testing in suspected cases, as well as carrier and prenatal diagnostic testing for individuals and couples worldwide.

Reach and significance of the impact

Since 1993, researchers at UoM have identified the molecular basis of 29 genetic diseases. Testing for these conditions is now offered in more than 140 laboratories in more than 30 countries worldwide.

As specific examples, testing of *PAX3*, *TCOF1*, *IRF6* and *C9ORF72* is offered in, respectively, 42, 28, 39 and 36 laboratories officially registered in Europe and the USA (S2, S3).

Considering individual tests in the UK only, for which numbers are most easily collated, screening for mutations in *TCOF1* has been undertaken in more than 500 patients in the Manchester and Oxford NHS diagnostic laboratories since 1997 (S4, S5), for mutations in *BEST1* in more than 250 patients in the Manchester NHS diagnostic laboratory since 2008 (S4), for mutations in *IRF6* in more than 170 patients at Great Ormond Street Hospital since 2005 (S6), for mutations in *SAMHD1* in more than 80 patients in the Leeds NHS diagnostic laboratory since 2009 (S7), and for mutations in *C9ORF72* in more than 170 patients in the UCL and Cardiff NHS laboratories since 2011 (S8).

The availability of a genetic test can obviate the need for other more invasive, expensive, and time-consuming investigations. Thus, in a recent report from Rare Disease UK (S9, p. 9), of 597 patients affected by a rare disease, one in five (20%) waited over five years, and over one in 10 (12%) waited over 10 years for a diagnosis. Related to this delay in diagnosis, over two thirds

(68%) of patients saw three or more doctors before their final diagnosis was made, and over one in five (22%) saw six or more doctors. Of extra significance, close to half (46%) of patients were given incorrect diagnoses before receiving their final diagnosis, and almost one third (30%) had received three or more misdiagnoses. These delays and misdiagnoses can be prevented for the 29 genetic diseases which UoM researchers have identified on a molecular basis.

Delays in diagnosis and multiple visits to doctors are a drain on health-care resources, which can be more efficiently used where the genetic basis of a disease is known, and a gene test is available. It is obvious, but worth stating, that the tortuous pathway to diagnosis described above can be tremendously stressful for patients and families.

Not only does the identification of the genetic basis of a disease allow for diagnostic testing, it also enables appropriate counselling of parents and other relatives and the provision of prenatal testing where that is considered relevant and appropriate. The importance of offering choice to families and couples in this situation is not easily measured, but must be understood and emphasised. Consider a couple with a child affected by a severe neurological condition (e.g. Aicardi-Goutières syndrome now known to be due to mutations in *SAMHD1*). Prior to 2009, the parents would have been told that there was a 1 in 4 chance of having another similarly affected child in a future pregnancy, but that no testing was available. They could either decide to have no further children, adopt, or 'take their chance' – a terrifying possibility for many couples. The advent of a genetic test allows couples in this situation to make informed choices – an advance the benefits of which are difficult to quantify but of undoubted importance.

5. Sources to corroborate the impact

S1. Department of Health. 2009 Annual Report of the Chief Medical Officer. London: Department of Health, 2010. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/AnnualReports/DH_113912
Detailing the importance of rare diseases to public health.

S2. http://www.orpha.net/consor/cgi-bin/ClinicalLabs_Search_Simple.php?lng=EN
Search engine of laboratories offering genetic testing (by gene / disease) across Europe.

S3. http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab?db=GeneTests
Search engine of laboratories offering genetic testing (by gene / disease) accredited in the USA.

S4. Corroborating email from Consultant Clinical Scientist, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust.

S5. Corroborating email from Principal Clinical Scientist, Oxford Medical Genetics Laboratories, Oxford University Hospitals NHS Trust.

S6. Corroborating email and data from Head of Molecular Genetics, NE Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Foundation Trust.

S7. Corroborating email from Research Scientist, Yorkshire Regional DNA Laboratory, Clinical Genetics Service, St James's University Hospital, Leeds.

S8. Corroborating email from Clinical Scientist, Institute of Medical Genetics, University Hospital of Wales. *Corroborating email from UCL also available.*

S9. Limb L, Nutt S, Sen A. Experience of Rare Diseases: An Insight from Patients and Families. London: Rare Disease UK, 2010. Available from: http://www.raredisease.org.uk/documents/RDUK-Family-Report.pdf
Detailed survey of the experiences of patients and families affected by rare diseases.