

Institution: University of Leeds		
Unit of Assessment: 1		
Title of case study: Transforming clinical management of inherited human diseases		
Period when the underpinning research was undertaken: 2004-2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Eamonn Sheridan Chris F Inglehearn	Professor of Clinical Genetics Professor of Molecular Ophthalmology	2000-present 1997-present
David Bonthron Colin A Johnson	Professor of Genetics Professor of Molecular and Medical Genetics	2000-present 2006-present
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Carmel Toomes Christine Diggle Manir Ali Jacquelyn Bond Sinisa Savic Yanick Crow C Geoffrey Woods	Associate Professor Senior Research Fellow Senior Research Fellow Senior Lecturer Clinical Associate Professor Clinical Senior Lecturer Wellcome Senior Fellow	2000-present 2001-present 1996-present 2001-present 2016-present 2006-2008 1998-2005
Period when the claimed impact occurred: 2013-2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>University of Leeds researchers have identified 109 genes which, when mutated, cause a range of clinical disorders including: developmental brain disorders, ciliopathies, renal and liver disease, immunodeficiency, cancer, and blindness. Linking the encoded proteins to inherited diseases has been key to genetics laboratories around the world developing new diagnostic technologies, and national and international screening programmes being implemented. In turn, this has resulted in thousands of diagnostic, carrier, and prenatal tests - enabling early diagnosis, better clinical management, and improved outcomes for patients. The understanding gained has underpinned successful clinical trials of novel therapies. Importantly, the work has led directly to better counselling and prenatal screening for families.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Seven per cent of the UK population, roughly 3.5 million people, live with a 'rare disease'. Over 6,000 rare diseases have been documented, of which around 80% have a genetic component. Twenty years ago genetic testing was only possible in a handful of cases, but a revolution in human genetics technology has led to a huge increase in our understanding of the genetic basis of these conditions, with researchers from Leeds playing a world-leading role.</p> <p>To address the huge clinical need to diagnose rare inherited disease for effective counselling and, in particular, tackle the specific local healthcare burden of rare recessive disease, researchers from the University of Leeds harnessed the power of genomics to accelerate the diagnostic process. In collaboration with families and clinical staff, researchers in Leeds identified more than 100 genes mutated in different inherited diseases.</p> <p>Exemplars of our research include discovering the role of nucleic acid intermediates in causing the inherited encephalopathy Aicardi-Goutiere syndrome (AGS) [1]; finding that mutations in the <i>PMS2</i> gene (which are difficult to detect due to sequence overlap with many pseudogenes) underlie a range of cancer syndromes, and identifying a number of other genes mutated in cancer [2]; determining the importance of primary cilia in health and disease [3]; identifying a series of genes involved in determining human brain size, neuronal development, and neuronal homeostasis [4,5]; identifying 10% of all the genes known to be mutated in inherited retinal dystrophy (IRD), as well as</p>		

genes involved in glaucoma and corneal dystrophies [6].

Autosomal dominant and X-linked conditions can often be solved through family studies, while the trio sequencing approach has proved a powerful technique for identifying *de novo* dominant variants, which account for approximately 40% of children with developmental delay. Leeds has used all of these approaches, but a particular focus for our research has been on autosomal recessive conditions. Our epidemiological investigations in the local Pakistani heritage community demonstrated conclusively, for the first time, a doubling of the risk of congenital disorders, due to the practice of consanguinity. This heightened risk results in an increase in autosomal recessive disorders. These risks were most recently highlighted in the 2016 Chief Medical Officer's report, [Generation Genome](#).

The many earlier diagnoses made possible by these discoveries have meant earlier intervention - which saves lives - as well as enabling informed counselling for patients and their families. These discoveries have provided novel insights into disease pathogenesis, and resulted in the description of novel clinical syndromes.

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

- [1] *Mutations involved in Aicardi-Goutières syndrome implicate SAMHD1 as regulator of the innate immune response*. Gillian I Rice, **Jacquelyn Bond**, Aruna Asipu, Rebecca L Brunette, Iain W Manfield, **Ian M Carr**, Jonathan C Fuller, Richard M Jackson, Teresa Lamb, Tracy A Briggs, **Manir Ali**, Hannah Gornall, Lydia R Couthard, Alec Aeby, Simon P Attard-Montalto, Enrico Bertini, Christine Bodemer, Knut Brockmann, Louise A Brueton, Peter C Corry, Isabelle Desguerre, Elisa Fazzi, Angels Garcia Cazorla, Blanca Gener, Ben C J Hamel, Arvid Heiberg, Matthew Hunter, Marjo S van der Knaap, Ram Kumar, Lieven Lagae, Pierre G Landrieu, Charles M Lourenco, Daphna Marom, Michael F McDermott, William van der Merwe, Simona Orcesi, Julie S Prendiville, Magnhild Rasmussen, Stavit A Shalev, Doriette M Soler, Marwan Shinawi, Ronen Spiegel, Tiong Y Tan, Adeline Vanderver, Emma L Wakeling, Evangeline Wassmer, Elizabeth Whittaker, Pierre Lebon, Daniel B Stetson, **David T Bonthron**, **Yanick J Crow**. *Nat Genet* 2009 Jul;41(7):829-32. DOI: [10.1038/ng.373](https://doi.org/10.1038/ng.373)
- [2] *Novel PMS2 pseudogenes can conceal recessive mutations causing a distinctive childhood cancer syndrome*. Michel De Vos, Bruce E Hayward, Susan Picton, **Eamonn Sheridan**, **David T Bonthron**. *Am J Hum Genet*. 2004 May;74(5):954-64. DOI: [10.1086/420796](https://doi.org/10.1086/420796)
- [3] *HEATR2 plays a conserved role in assembly of the ciliary motile apparatus*. **Christine P Diggle**, Daniel J Moore, Girish Mali, Petra zur Lage, Aouatef Ait-Lounis, Miriam Schmidts, Amelia Shoemark, Amaya Garcia Munoz, Mihail R Halachev, Philippe Gautier, Patricia L Yeyati, **David T Bonthron**, **Ian M Carr**, Bruce Hayward, **Alexander F Markham**, Jilly E Hope, Alex von Kriegsheim, Hannah M Mitchison, Ian J Jackson, Bénédicte Durand, Walter Reith, **Eamonn Sheridan**, Andrew P Jarman, Pleasantine Mill. *PLoS Genet*. 2014 Sep 18;10(9):e1004577. DOI: [10.1371/journal.pgen.1004577](https://doi.org/10.1371/journal.pgen.1004577)
- [4] *Loss-of-function mutations in MICU1 cause a brain and muscle disorder linked to primary alterations in mitochondrial calcium signaling*. Clare V Logan, György Szabadkai, Jenny A Sharpe, David A Parry, Silvia Torelli, Anne-Marie Childs, Marjolein Kriek, Rahul Phadke, **Colin A Johnson**, Nicola Y Roberts, **David T Bonthron**, Karen A Pysden, Tamieka Whyte, Iulia Munteanu, A Reghan Foley, Katarzyna Szymanska, Subaashini Natarajan, Zakia A Abdelhamed, Joanne E Morgan, Helen Roper, Gijs W E Santen, Erik H Niks, W Ludo van der Pol, Dick Lindhout, Anna Raffaello, Diego De Stefani, Johan T den Dunnen, Yu Sun, Ieke Ginjaar, Caroline A Sewry, Matthew Hurles, Rosario Rizzuto, UK10K Consortium; Michael R Duchen, Francesco Muntoni, **Eamonn Sheridan**. *Nat Genet*. 2014 Feb;46(2):188-93. DOI: [10.1038/ng.2851](https://doi.org/10.1038/ng.2851)
- [5] *De novo CCND2 mutations leading to stabilization of cyclin D2 cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome*. Ghayda Mirzaa, David A Parry, Andrew E Fry, Kristin A Giamanco, Jeremy Schwartzentruber, Megan Vanstone, Clare V Logan, Nicola Roberts, **Colin A Johnson**, Shawn Singh, Stanislav S Kholmanskikh, Carissa Adams, Rebecca D Hodge, Robert F Hevner, **David T Bonthron**, Kees P J Braun, Laurence Faivre, Jean-Baptiste Rivière, Judith St-Onge, Karen W Gripp, Grazia Ms Mancini, Ki Pang, Elizabeth Sweeney, Hilde van Esch, Nienke Verbeek, Dagmar Wiczorek, Michelle Steinraths, Jacek Majewski, FORGE Canada Consortium; Kym M Boycot, Daniela T Pilz, M Elizabeth Ross, William B Dobyns, **Eamonn G Sheridan**. *Nat Genet*. 2014 May;46(5):510-515. DOI: [10.1038/ng.2948](https://doi.org/10.1038/ng.2948)

[6] Biallelic mutations in the autophagy regulator DRAM2 cause retinal dystrophy with early macular involvement. Mohammed E El-Asrag, Panagiotis I Sergouniotis, Martin McKibbin, Vincent Plagnol, **Eamonn Sheridan**, Naushin Waseem, Zakia Abdelhamed, Declan McKeefry, Kristof Van Schil, James A Poulter, UK Inherited Retinal Disease Consortium; **Colin A Johnson**, **Ian M Carr**, Bart P Leroy, Elfride De Baere, **Chris F Inglehearn**, Andrew R Webster, **Carmel Toomes**, **Manir Ali**. Am J Hum Genet. 2015 Jun 4;96(6):948-54. DOI: [10.1016/j.ajhg.2015.04.006](https://doi.org/10.1016/j.ajhg.2015.04.006)

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

Worldwide, rare diseases affect 3.5–5.9% of the population, equivalent to around 300 million people. In the UK this figure is higher, with around 3.5 million people (7% of the population) affected. Babies and children are most likely to be affected, with as many as 30% of those who have a rare disease dying before their fifth birthday. Our research has identified 109 genes which, when mutated, cause diverse rare human conditions. This has resulted in laboratories across Europe screening for these genes, the identification of these genes on the UK national test directory, and the successful completion of clinical trials involving these genes **[A]**.

Influencing new diagnostic technologies and screening programmes worldwide

Our research has had a profound impact on the development of new diagnostic technologies, and on national and international screening programmes globally. The Orphanet website **[B]** lists the European Medical Laboratories that provide diagnostic tests for specified genes or diseases. If we take the representative genes that were highlighted in section 3, Orphanet shows that *SAMHD1* was tested in 54 laboratories, *PMS2* was tested in 183 laboratories, *HEATR2* in 7 laboratories, *MICU1* in 15 laboratories, *CCND2* in 11 laboratories, and *DRAM2* in 11 laboratories. Other notable genes implicated in disease by our researchers and widely screened by European laboratories include *CEP290* (142 laboratories), *TMEM67* (93 laboratories), and *LRP5* (86 laboratories).

Commercial sensitivities mean that the precise number of tests cannot be calculated, but we surveyed 134 European genetic testing laboratories, which allowed us to estimate that over 50,000 tests were carried out in 2019 in Europe alone for genes implicated through our research **[C]**.

The worldwide figure is likely to be much higher, and major genetic sequencing companies globally are testing for genes associated with disease through our research. For example, the Illumina sequencing company (revenue USD3,543 million in 2019) included the genes *TET2* and *PMS2* in their widely used Illumina TruSight Oncology 500 NGS assay launched in 2018 **[D]**. The world-renowned geneticist and President of US company 'PreventionGenetics', said:

"Tests for all of the genes listed [SAMHD1, PMS2, ASPM, TMEM67, NMNAT1] are on our test menu.... We have identified many patients who carry pathogenic variants in these genes" **[E_i]**.

The Director of Spanish biotechnology company, Sistemas Genómicos, said:

"These genes are crucial in genetic diagnosis, and in our experience, fundamental in this field due to the relatively high number of patients suffering from these genetic conditions. Specifically, in the oncogenetics area, the study of PMS2 is very important....During the year 2019, we carried out 568 genetic analyses, which included this gene. Some of these studies confirmed the suspected clinical diagnosis, which allowed offering [sic] an adequate genetic counselling and appropriate medical management to the patient and their families" **[E_ii]**.

The extent of the impact can also be seen within government documentation on commissioning of genetic tests. For example, the UK National Genomic Test Directory specifies which genomic tests are commissioned by the NHS in England, and lists a core set of genes that must be tested in NHS laboratories. Ninety eight of the genes associated with rare diseases by our researchers since 2000 are on the UK list **[F]**, which features a total of 5851 genes (i.e. we have contributed 1.67% of identified genes). The President of the UK Clinical Genetics Society, confirmed that:

"The over one hundred genes linked to human inherited diseases by researchers in Leeds are screened regularly in laboratories across the UK to support clinical diagnosis for patients" **[E_iii]**.

The Clinical Lead for the DECIPHER and the Deciphering Developmental Disorders project based at the Wellcome Sanger Institute, Hinxton, acknowledged that:

“tests for dozens of genes linked to human inherited diseases by researchers in Leeds.... account for a significant and important contribution to our diagnostic yield” [E_iv].

The impact of our research is further evidenced by its influence within major genomics projects. For example, the 100,000 Genomes Project, completed in 2018, sequenced 100,000 whole human genomes from patients with rare diseases and their families, and patients with common cancers. The Clinical Director of Genomics England, confirmed that the genes we identified:

“accounted for a significant proportion of activity across the 100,000 Genomes Project” [E_v].

The co-lead investigator of the Scottish Genomes partnership said that:

“The many rare disease genes discovered by researchers in Leeds played a key role in helping to understand causes, diagnosis and potential treatments for such inherited diseases” [E_vii].

New understanding underpins clinical trials of novel therapies

The genetic research findings from Leeds have allowed clinicians to compare patients from different centres who have variants in a single gene. This has guided clinical decision-making, as well as the novel research insights informing clinical trial design. Examples include drug trials in patients with *TREX1* and *PLA2G6* mutations; personalised medicine approaches and drug trials for specific cancer subgroups (including *PMS2* and *TET2* mutation carriers); *CEP290* variants targeted by antisense oligo therapy; a vaccine targeting cells over-expressing TBXT to treat certain tumour types; drug, dietary and physiotherapy approaches being tested in Primary Ciliary Dyskinesia (PCD) patients; and the use of anti-ADAM9 antibodies as a tumour therapy [G]. For example, a clinical trial of azithromycin maintenance therapy in PCD, caused by mutations in six of the genes implicated through Leeds research, showed this halved the rate of respiratory exacerbations [H]. In addition, our research on AGS, caused by mutations in *SAMHD1* and four other genes (all identified by Leeds researchers) led directly to a clinical trial of the drug baricitinib, which proved effective in improving neurologic outcomes in patients [I].

Improved health and wellbeing through diagnosis, counselling and better treatment

Discovery of the 109 genes through research at the University of Leeds has enabled early diagnosis, better management, and improved outcomes for patients, and better counselling and prenatal screening for families. The importance of this impact was highlighted by inherited retinal dystrophy (IRD) patients (19 genes implicated through Leeds research) who reported that they strongly supported the provision of publicly funded genetic testing. The IRD patients valued the greater understanding and knowledge about the genetic basis of their condition, and valued the resulting early access to emerging therapies. The patients also reported benefits to family members and future generations, as well as to society in general [J].

Our research has also allowed charities to support families living with rare conditions. According to the CEO of Unique (a charity supporting people with rare chromosome and gene disorders):

*“The [Leeds] research has provided important insights that directly benefit those affected by genetic mutations. In particular, the discovery that blindness is due to mutations in splicing factors *PRPF8* and 3, the identified relationship between retinal vascular disease and *TSPAN12* variants, and the finding of diverse immunological phenotypes due to *CARD11* mutations has allowed a genetic diagnosis to be made – diagnoses which directly improve the quality of life for affected individuals within the UK and throughout the world” [E_vii].*

The CEO of Cerebra, a charity that helps children with genetic brain conditions, said:

“....the fundamental genetics research at the University of Leeds has led to improvements in genetic identification that have significantly improved the lives of our members and have given them and us new hope for the future..... This new understanding allows our members to obtain a

genetic diagnosis, which gives them a much better idea of what the future holds for them, something in which we and they place great value. It also gives information about risk for other family members and future generations, is the first step towards better treatments and new therapies and is an essential prerequisite for recruitment to clinical trials” [E_viii].

The CEO of Retina UK, a patient-led charity supporting people with retinal diseases, confirmed:

“the Leeds Vision Research Group has played a world-leading role in the drive towards a genetic diagnosis for everybody with inherited retinal disease. Knowledge of their genotype is something our members value very highly indeed, since it is the essential first step in the journey towards understanding their condition and accessing the best possible treatment” [E_ix].

The Board of the Ciliopathy Alliance have recognised the vital importance of the Leeds research and the impact it has had on families affected by ciliopathies:

“Leeds geneticists have excelled over the past 10 years, identifying over 100 genes linked to inherited diseases. These include 29 genes that, when mutated, cause ciliopathies. This is a huge contribution to the worldwide human genetics revolution from a single centre. Linking genes with inherited diseases means patients and their families can plan their lives knowing how their condition is likely to progress and what risk it poses to relatives” [E_x].

The impact of this research is best expressed by the patients who benefit from the findings. For example, a patient with VEXAS syndrome (due to a somatic mutation in *UBA1*) wrote that:

“For four years I have battled with a progressive illness... Last year I was told that I was unlikely to survive more than another 6-12 months, and to complete a DNR Form, write my will, etc. It therefore came as a massive relief to discover at the end of last year that your team had described a syndrome that exactly matched my own illness.... I feel that my symptoms are benefiting from a combination of steroids and a monoclonal antibody” [K].

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

- [A] Collated data of 109 genes discovered by University of Leeds researchers and the corresponding number of European laboratories screening these genes, presence on UK national test directory, and clinical trials involving genes
- [B] Orphanet Portal. European reference portal for information on rare diseases and orphan drugs for all audiences. <https://www.orpha.net/consor/cgi-bin/index.php>
- [C] Compiled responses from survey of 134 European Genetic Screening laboratories
- [D] TruSight™ Oncology 500 and TruSight Oncology 500 High-Throughput Data Sheet
- [E] Testimonials from leading individuals/patient organisations involved in Human Genetics: i) President of PreventionGenetics, USA; ii) Director, Sistemas Genómicos, Spain; iii) President of UK Clinical Genetics Society; iv) Clinical Lead for the DECIPHER and Deciphering Developmental Disorders project; v) Clinical Director of Genomics England; vi) Co-Lead of the Scottish Genomes Partnership; vii) CEO, Unique; viii) CEO, Cerebra; ix) CEO, Retina UK; x) Board of the Ciliopathy Alliance
- [F] National Genomic Test Directory, NHS England
- [G] Details of clinical trials available at ClinicalTrials.gov. <https://www.clinicaltrials.gov/>
- [H] Kobbernagel HE, Buchvald FF, Haarman EG, et al. Efficacy and safety of azithromycin maintenance therapy in primary ciliary dyskinesia (BESTCILIA): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2020; 8:493-505. DOI: [10.1016/S2213-2600\(20\)30058-8](https://doi.org/10.1016/S2213-2600(20)30058-8)
- [I] Vanderver A, Adang L, Gavazzi F, et al. Janus Kinase Inhibition in the Aicardi-Goutières Syndrome (Clinical Trial). *N Engl J Med* 2020; 383:986-989. DOI: [10.1056/NEJMc2001362](https://doi.org/10.1056/NEJMc2001362)
- [J] Willis TA, Potrata B, Ahmed M, et al. Understanding of and attitudes to genetic testing for inherited retinal disease: a patient perspective. *Br J Ophthalmol* 2013; 97:1148-54. DOI: [10.1136/bjophthalmol-2013-303434](https://doi.org/10.1136/bjophthalmol-2013-303434)
- [K] Patient testimonial, anonymised