

<b>Institution: The University of Edinburgh</b>
<b>Unit of Assessment: 1</b>
<b>Title of case study: G: Diagnosis from gene discovery – developmental disorders of eye, brain, nerve and skeleton</b>
<p><b>1. Summary of the impact</b> (indicative maximum 100 words)</p> <p><b>Impact:</b> Health and welfare; policy and guidelines; public engagement. The identification of &gt;20 genes linked to human developmental and childhood degenerative disorders.</p> <p><b>Significance:</b> Definitive diagnosis is essential for genetic counselling, prenatal screening and postnatal management.</p> <p><b>Beneficiaries:</b> People with developmental disorders and their families, prospective parents, the NHS and healthcare delivery organisations; public understanding of genetic disorders.</p> <p><b>Attribution:</b> Researchers from UoE identified/characterised all the genes described, and their mutation in disease.</p> <p><b>Reach:</b> Worldwide: these developmental disorders affect thousands of people. Genetic tests established as a result of the research are provided for people from 35 countries on all continents.</p>
<p><b>2. Underpinning research</b> (indicative maximum 500 words)</p> <p>The development of genetic tests to underpin accurate diagnosis, genetic counselling and prospective management in developmental disorders represents a major translational focus for the MRC Human Genetics Unit (HGU) within UoE.</p> <p>Developmental disorders are significant clinical problems that result from perturbation of embryogenesis or early brain development. At least 3% of live-born babies have a developmental disorder that will have a deleterious impact on their life. The majority of these disorders are genetically determined. An understanding of developmental disorders, which is critical for adequate diagnosis, prognosis and management, requires both knowledge of the genes involved and how the gene products function as effectors of the specific developmental processes. The identification and characterisation of these monogenic disorders exemplifies well the wide range of impacts that result from apparently “basic” research.</p> <p>Scientists from the MRC HGU, including Professors David FitzPatrick (Programme Leader, UoE, 2000–present), Veronica van Heyningen (Programme Leader, UoE, 1977–2012; now Emeritus), Andrew Jackson (Programme Leader, UoE, 2005–present) and Peter Brophy (Professor of Anatomy, UoE, 1995–present) have directly contributed to the identification and functional characterisation of more than 20 genes associated with human developmental and degenerative disorders. Key examples include:</p> <p><b>Eye:</b> Between 2000 and 2012, FitzPatrick and van Heyningen identified abnormalities in the <i>SOX2</i>, <i>OTX2</i>, <i>PAX6</i>, <i>STRA6</i>, <i>NF1</i> and <i>SMOC1</i> genes as the causes of serious human eye malformations, notably anophthalmia (absent eye), microphthalmia (small eye) and coloboma (failure of optic fissure closure) [e.g., 3.1, 3.2]. van Heyningen linked haploinsufficiency of <i>PAX6</i> to cerebral malformation and olfactory dysfunction (2001) [3.3] and FitzPatrick identified <i>SATB2</i> as the cleft palate gene (2003). FitzPatrick undertook studies that showed the causative role of mutations in <i>DHCR24</i> in desmosterolosis, an autosomal recessive disorder of cholesterol biosynthesis (2001) and in studies that associated disruption of the <i>ST5</i> gene with mental retardation and multiple congenital anomalies (2010).</p>

**Skeleton:** More recently, FitzPatrick's work has led to the identification of mutations in *CEP57* that cause mosaic variegated aneuploidy syndrome (2011), the discovery that gain-of-function mutations in *ARHGAP31*, a Cdc42/Rac1 GTPase regulator, cause syndromic cutis aplasia and limb anomalies (2011), and that a rare intragenic deletion within the region encoding the NIPBL protein is associated with atypical facial appearance and growth pattern in Cornelia de Lange Syndrome (2012).

**Brain:** The work of Jackson since 2005 has been essential to the identification of seven microcephalic primordial dwarfism genes (*ORC1*, *ORC4*, *ORC6*, *CDT1*, *CDC6*, *PCNT* and *CEP152*) that regulate organism size and cerebral cortex volume [e.g., 3.4]. Jackson and colleagues also showed that mutations in genes encoding the DNA exonuclease TREX1 and ribonuclease H2 subunits (*RNASEH2A*, *RNASEH2B*, *RNASEH2C*) cause Aicardi-Goutières syndrome, a congenital immune-mediated neurodevelopmental disorder [e.g., 3.5].

**Nerve:** Brophy and colleagues discovered that a mutation in *PRX*, encoding periaxin, is responsible for a form of Charcot-Marie-Tooth (CMT) disease, a disorder of the peripheral nervous system characterised by progressive loss of muscle tissue and touch sensation (2001) [3.6].

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

The references below represent selected examples from the large body of published work.

- 3.1 Fantès J, Ragge N, Lynch S,...van Heyningen V, FitzPatrick D. Mutations in *SOX2* cause anophthalmia. *Nat Genet.* 2003;33:461–3. DOI: 10.1038/ng1120.
- 3.2 Ragge N, Brown A, Poloschek C,...Fitzpatrick D, van Heyningen V, Hanson I. Heterozygous mutations of *OTX2* cause severe ocular malformations. *Am J Hum Genet.* 2005;76:1008–22. DOI: 10.1086/430721.
- 3.3 Sisodiya S, Free S, Williamson K,...van Heyningen V. *PAX6* haploinsufficiency causes cerebral malformation and olfactory dysfunction in humans. *Nat Genet.* 2001;28:214–6. DOI: 10.1038/90042.
- 3.4 Bicknell L, Bongers E, Leitch A,...Jackson A. Mutations in the pre-replication complex cause Meier-Gorlin syndrome. *Nat Genet.* 2011;43:356–9. DOI: 10.1038/ng.775.
- 3.5 Crow Y, Leitch A, Hayward B,...Jackson A. Mutations in genes encoding ribonuclease H2 subunits cause Aicardi-Goutières syndrome and mimic congenital viral brain infection. *Nat Genet.* 2006;38:910–6. DOI: 10.1038/ng1842.
- 3.6 Guilbot A, Williams A, Ravisé N,... Brophy P, et al. A mutation in periaxin is responsible for CMT4F, an autosomal recessive form of Charcot-Marie-Tooth disease. *Hum Mol Genet.* 2001;10:415–21. DOI: 10.1093/hmg/10.4.415.

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

#### Impact on health and welfare and clinical services

Below, three groups of genetic disorders identified and characterised by UoE researchers, and their specific impact on aspects of clinical management/service, are described in greater detail. Although rare, inherited developmental disorders are distributed across the world and are devastating for patients and their families. Crucially, the identification of causative mutations permits effective genetic counselling: a cornerstone of the family management of each of these disorders. UoE research findings have directly resulted in the availability of clinical tests (including some offered in-house, see below) to clarify genetic risk and have enabled diagnostic and/or prenatal testing for these devastating disorders.

Genetic testing and pre-natal screening - eye disorders: Developmental eye disorders occur in approximately five per 10,000 live births and are responsible for around 25% of severe visual impairments in childhood. Diagnosis of the primary ocular disorder may be self-evident, but >50%

of cases manifest distinct systemic abnormalities, such as developmental delay, kidney or heart defects and cleft lip or palate. A full diagnosis including identification of causative genetic abnormalities is essential to define the visual potential of the child, inform the counselling of the parents and establish prospective management, including the possible need for special educational placement, with respect to the long-term prognosis.

Tests for mutations in the *SOX2*, *OTX2* and *PAX6* genes are now offered by multiple labs in the UK and internationally including the USA, Germany, France, Denmark and Switzerland [5.1]. Prenatal genetic testing for anomalies in these genes (that allows informed decision on pregnancy) is offered by some laboratories, e.g., GeneDx in the USA. Tests for *STRA6*, *NF1* and *SMOC1* gene abnormalities are available in the UK and internationally [5.1].

Molecular diagnosis informing effective clinical management and counselling - childhood-onset neurological disease: CMT is one of the most common inherited neurological disorders affecting approximately 1 in 2,500 people, equating to approximately 23,000 people in the UK and 125,000 people in the USA. While Aicardi-Goutières syndrome represents a rarer disorder, together, these conditions demonstrate the distinct ways in which clinical diagnosis can be facilitated by accurate genetic testing. Both conditions are incurable and early diagnosis is instrumental for clinical management and counselling. Genetic testing for causative mutations is important in CMT because it does not represent a single disorder, but a group of conditions that are superficially clinically similar, but with widely differing modes of inheritance and penetrance. Effective genetic counselling has only become possible with the application of genetic testing [5.2]. In contrast, Aicardi-Goutières syndrome poses a rather different clinical challenge, as it phenocopies congenital viral infections such as CMV, rubella and transplacentally acquired HIV. Given the substantial risk of recurrence in subsequent pregnancies, molecular diagnosis of Aicardi-Goutières syndrome is essential for counselling and also key to the provision of prenatal diagnosis in subsequent pregnancies.

Tests for mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C* (Aicardi-Goutières syndrome) and *PRX* (CMT) are offered in several countries including the UK, USA, Germany, Spain, Austria, France and Italy [5.1].

Genetic testing to establish effective prospective management - growth syndromes: Primordial dwarfism is a rare disorder resulting in extreme pre- and postnatal growth failure, such that people with this group of conditions are often described as ‘the smallest people in the world’. The identification of the genetic basis has had a significant impact on clinical management. In particular, it has helped to define those with resulting syndromes who are at risk of insulin-resistant diabetes mellitus, and of neurovascular complications, enabling specific targeting of appropriate surveillance [5.3].

Tests for mutations in primordial dwarfism genes are available in the UK, USA and the Netherlands [5.1]. In the UK they are offered directly by Jackson’s laboratory, and since 2008 Jackson’s lab has performed molecular gene testing on over 400 patients from 35 countries worldwide.

### **Impact on policy and guidelines**

In the report “Genetic ophthalmology in focus: a needs assessment and review of specialist services for genetic eye disorders” published in April 2008 (to which FitzPatrick and van Heyningen contributed), the Foundation for Genomics and Population Health indicated how NHS ophthalmology services needed to change in response to the opportunities offered by genetic science. The foundation placed mutation detection in severe developmental eye disorders on the list of main gaps and perceived priorities for testing [5.4]. This report has had major impact on UK Government policy: for example, it was analysed by the House of Lords’ Science and Technology Committee in 2008–2009 [5.5], leading to new recommendations and improved services. Notably, van Heyningen was an expert witness to the Committee on April 30<sup>th</sup>, 2008 [5.5].

**Impact on society and public engagement**

Genetic testing is recommended by diverse societies and organisations and is promoted on their websites, e.g., the International Children's Anophthalmia Network [5.6]. In addition, because people with primordial dwarfism are among the shortest people in the world, this small group has a disproportionately large impact on public engagement with developmental disorders. Primordial dwarfism and its genetic causes have been discussed in several high-profile television documentaries that generated huge public interest, e.g., "The Tiniest Boy in Britain" (2011) and "21 and 3ft tall" (2013). Notably, the latter included an interview with Jackson and describes research in his lab [5.7].

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

- 5.1 Example lists of multiple laboratories from up to 12 countries providing genetic tests for the genes mentioned in the text. <http://www.orpha.net/consor/cgi-bin/index.php> (under: directory of medical laboratories providing diagnostic tests). Further examples can be found at <http://www.ncbi.nlm.nih.gov/qtr/tests/>.
- 5.2 Siskind C, Panchal S, Smith C, et al. A review of genetic counselling for Charcot Marie Tooth disease (CMT). *J Genet Couns.* 2013;22:422–36. DOI: 10.1007/s10897-013-9584-4.
- 5.3 Semple R, Savage D, Cochran E, et al. Genetic syndromes of severe insulin resistance. *Endocr Rev.* 2011;32:498–514. DOI: 10.1210/er.2010-0020.
- 5.4 Foundation for Genomics and Population Health (PHG Foundation) report (April 2008). "Genetic ophthalmology in focus: a needs assessment and review of specialist services for genetic eye disorders". <http://www.phgfoundation.org/file/4199>.
- 5.5 Genomic medicine: 2nd report of session 2008–2009, Volume II: Evidence. Great Britain Parliament, House of Lords, Science and Technology Committee. <http://www.publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/107ii.pdf>.
- 5.6 International Children's Anophthalmia Network website. <http://www.anophthalmia.org/diagnosis/>.
- 5.7 Daily Mail online (2<sup>nd</sup> July 2013). "Aged 21 but just 35 inches tall: The man with a rare form of dwarfism which makes him the size of a three-year-old". <http://www.dailymail.co.uk/health/article-2353418/Nick-Smith-The-man-rare-form-dwarfism-makes-size-year-old.html>. [Article about the Channel 5 documentary.]