Institution: University of Manchester

Unit of Assessment: UoA05

Title of case study: Identification of genes and mutations in genetic skeletal diseases leads to improved diagnosis and counselling through an international clinical and DNA diagnostic network

1. Summary of the impact

Genetic skeletal diseases (GSDs) are an extremely diverse and complex group of genetic diseases that affect the development of the skeleton. Although individually rare, as a group of related genetic diseases they have an overall prevalence of at least 1 per 4,000 children, which extrapolates to a minimum of 225,000 people in the European Union. This burden in pain and disability leads to poor quality of life and high healthcare costs. GSDs are difficult diseases to diagnose and there are currently no treatments, therefore, arriving at a confirmed diagnosis is vital for clinical management, psycho-social support and genetic counselling.

Research conducted at the University of Manchester (UoM) has had a major influence on establishing the correct diagnosis of specific GSDs by the discovery of causative genes and mutations and the subsequent development of accurate and reliable DNA testing protocols. This has significantly improved both accuracy of, and access to, genetic testing in the UK, Europe and worldwide.

2. Underpinning research

This impact case is the direct result of research that took place at UoM from 1996 to 2012. The key researchers were:

Dr Michael Briggs (Senior Research Fellow, 1996-2012)
Dr Kathryn Chapman (Post-Doctoral Research Associate, 1999-2001)
Dr Paul Holden (Research Associate / Post-Doctoral Research Associate, 1996-2001)
Dr Gail Jackson (Post-Doctoral Research Associate, 2002-2010)

The aim of the original research programme was the identification and characterisation of the genes and mutations responsible for a diverse range of GSDs, including pseudoachondroplasia (PSACH), multiple epiphyseal dysplasias (MED) and various spondylo-epi-metaphyseal dysplasias . This information was subsequently used to establish DNA diagnostic protocols and a pan-European diagnostic network for GSDs (2002 to date). The key discoveries were as follows:

- Discovery that mutations in the gene encoding matrilin-3 (*MATN3*) cause a form of autosomal dominant MED (EDM5) [1] with the subsequent identification of a definitive range of disease causing mutations [2].
- Confirmation that mutations in the genes encoding type IX collagen [3] and cartilage oligomeric matrix protein (COMP) [4] result in a wide range of phenotypes within the PSACH-MED disease spectrum.
- The identification and characterisation of this definitive range of disease causing mutations in these genes allowed development of accurate molecular diagnosis protocols that also have pre-symptomatic and pre-natal applications [4-6].

A DNA diagnostic service for PSACH-MED phenotypes was developed and subsequently improved [4-6]. The concurrent establishment of a trans-national diagnostic network has improved diagnosis and mutation detection rates for these diseases. The on-line case management system allows clinicians to submit cases directly to the European Skeletal Dysplasia Network (ESDN) from anywhere in the world, thereby expediting access to expert advice.

3. References to the research

The research produced a complementary series of publications, many of which are in high impact journals and/or leading journals in the field (ISI Journal Rankings 2010 - Genetics and Heredity).

1. **Chapman K.L.**, Mortier G.R., Chapman K., Loughlin J.A., Grant M.E., **Briggs M.D**. (2001) Mutations in the region encoding the von Willebrand factor A domain of matrilin-3 are

associated with multiple epiphyseal dysplasia. *Nat Genet.* 28 (4). p. 393-396. DOI: 10.1038/ng573

2. **Jackson G.C.**, Barker F.S., Jakkula E., Czarny-Ratajczak M., Makitie O., Cole W.G., Wright M.J., Smithson S.F., Suri M., Rogala P., Mortier G.R., Baldock C., Wallace A., Elles R., Ala-Kokko L., **Briggs M.D**. (2004) Missense mutations in the beta strands of the single A-domain of matrilin-3 result in multiple epiphyseal dysplasia. *J Med Genet.* 41 (1). p. 52-59. DOI:10.1136/jmg.2003.011429

3. **Holden P.**, Canty E.G., Mortier G.R., Zabel B., Spranger J., Carr A., Grant M.E., Loughlin J.A., **Briggs M.D.** (1999) Identification of novel pro-alpha2(IX) collagen gene mutations in two families with distinctive oligo-epiphyseal forms of multiple epiphyseal dysplasia. *Am J Hum Genet*. 65 (1). p.31-38. DOI: 10.1086/302440

4. Kennedy J., **Jackson G.C.**, Ramsden S., Taylor J., Newman W., Wright M.J., Donnai D., Elles R., **Briggs M.D**. (2005) COMP mutation screening as an aid for the clinical diagnosis and counselling of patients with a suspected diagnosis of pseudoachondroplasia or multiple epiphyseal dysplasia. *Eur J Hum Genet.* 13 (5). p.547-555. DOI: 10.1038/sj.ejhg.5201374

5. Zankl A., **Jackson G.C.**, Crettol L.M., Taylor J., Elles R., Mortier G.R., Spranger J., Zabel B., Unger S., Merrer M.L., Cormier-Daire V., Hall C.M., Wright M.J., Bonafe L., Superti-Furga A., **Briggs M.D**. (2007) Preselection of cases through expert clinical and radiological review significantly increases mutation detection rate in multiple epiphyseal dysplasia. *Eur J Hum Genet.* 15 (2). p. 150-154. DOI: 10.1038/sj.ejhg.5201744

6. **Jackson G.C.**, Mittaz-Crettol L., Taylor J.A., Mortier G.R., Spranger J., Zabel B., Le Merrer M., Cormier-Daire V, Hall C.M., Offiah A., Wright M.J., Savarirayan R., Nishimura G., Ramsden S.C., Elles R., Bonafe L., Superti-Furga A., Unger S., Zankl A., **Briggs M.D**. (2012) Pseudoachondroplasia and multiple epiphyseal dysplasia; a 7-year comprehensive analysis of the known disease genes identify novel and recurrent mutations and provides an accurate assessment of their relative contribution. *Hum Mutat.* 33 (1). p.144-157. DOI: 10.1002/humu.21611

4. Details of the impact

Context

GSDs are an extremely diverse and complex group of rare genetic diseases, for which diagnosis can be difficult for the non-expert. There are more than 450 unique and well-characterised phenotypes that range in severity from relatively mild to severe and terminal forms. The accurate diagnosis of a specific GSD therefore usually necessitates several types of investigation such as review of the child's medical and family history, physical examination, genetic testing and radiological evaluation. Moreover, genetic mutational analysis plays a pivotal role in establishing the correct diagnosis and in facilitating clinical management, accurate risk assessment and genetic counselling for family members. Before Brigg's discoveries, the diagnosis of some GSDs (i.e. PSACH-MED-SEMD) relied entirely upon clinical and radiological methods. Brigg's research introduced a completely new paradigm in rare disease diagnosis by demonstrating that a trans-national clinical and molecular diagnosis network (ESDN) could dramatically improve patient access to expert diagnosis for GSDs and also increase mutation detection rates.

Pathways to impact

Development of gene specific DNA tests for PSACH-MED

The identification of causative genes and mutations for PSACH-MED, namely *COMP*, *MATN3* and the type IX collagen genes (*COL9A1-3*), allowed the development of gene specific DNA diagnostic tests. These tests were originally offered to 5-10 clinicians on a 'research basis' by the Briggs laboratory, however, the un-sustainability of this approach in a non-accredited laboratory, led to the inclusion of these diagnostic tests in the portfolio of the Regional Molecular Genetics Laboratory at St Mary's Hospital in Manchester. Initial funding for this service was provided by the PPP Healthcare Trust (2001-2003) and then subsequently through the European Commission 5th and 6th Framework Programmes (2002-2010). The success of the PSACH-MED diagnostic service allowed a sustainable financial model to be applied in early 2010 and the referring clinicians now

pay for all testing via the NHS or health insurance (overseas referrals).

Establishment of the first trans-national diagnostic network for rare GSDs

The European Skeletal Dysplasia Network (ESDN) was first established in January 2002 with a grant from the European Commission with a remit to develop an integrated research and diagnostic network for skeletal dysplasias. This was the **first** trans-national diagnostic network for any genetic disease grouping.

Reach and significance of the impact

Development of gene specific DNA tests for PSACH and MED

Specific DNA tests that allow earlier and more accurate diagnosis (also prenatal and predictive testing) are now available to UK families through the Regional Genetic Laboratory (Manchester) [A] and these protocols have also been widely adopted in other testing laboratories across Europe [B], North America [C] and elsewhere. Indeed, there are now 19 diagnostic centres in Europe [B], three in North America and one centre in Korea [C] offering DNA testing for PSACH-MED. In most of these centres, the current service is still based on Brigg's screening protocols and molecular diagnosis has been provided to 100s of patients with PSACH, MED and related diseases. For example, representative sampling of COMP diagnostic testing performed by three referral laboratories located in different geographical areas has revealed the following number of tests were performed [D-F]:

	2008	**2009**	**2010**	**2011**	**2012**
USA (Gaithersburg)	38	29	20	15	11
Korea (Seoul)	11	69	20	20	3
UK (Manchester)	23	46	32	21	38

A similar number of tests were also performed for *MATN3* and the type IX collagen genes. These numbers do not include the testing of additional family members for prenatal and predictive purposes, which plays a major role in providing counselling and reproductive options to families.

From this 5-year sampling it is clear that there was a consistent number of tests performed each year and that the adoption of a charging policy in Manchester at the beginning of 2010 did not drastically reduce the numbers of referrals, thereby demonstrating the clinical requirement and utility of these tests. In summary, the availability of these reliable and rapid genetic tests has had a major impact on the delivery of genetic healthcare to patients worldwide.

Undiagnosis or misdiagnosis causes considerable psychosocial problems. Having the correct genetic diagnosis aids prenatal testing and guides in predictive and prognostic aspects.

Establishment of the first trans-national diagnostic network for rare GSDs

The European Skeletal Dysplasia Network (ESDN) was one of the first networks of expertise in the field of rare diseases to use information and communications technology (ICT) tools for the purposes of tele-expertise and medical diagnosis [G]. From September 2003, ESDN has received over 1600 referrals through the on-line Case Manager and 450 users have accessed the ESDN Case Manager from 45 different countries worldwide. For example, the following referrals were made in the period 2008-2012 (inclusive) [H]:

	2008	**2009**	**2010**	**2011**	**2012**
Number of referrals	190	217	179	170	176

Referrals in 2008-2012 have come from regional genetics centres in 20 UK cities (240 patients), 23 different European countries (469 patients) and 13 countries outside of Europe (223 patients) including [H]:

Country	Australia	Brazil	India	Iran	Israel	Malaysia	Pakistan	Saudi Arabia	South Africa	Taiwan	Turkey
Number of referrals	20	6	108	9	17	2	6	38	3	6	12

Interestingly, the period 2008-2011 has seen a significant increase in referrals from emerging economies. For example, ESDN received 8 referrals from India between 2003-2007 and this has increased dramatically to 108 during the 4-year period 2008-2012 [H], confirming that ESDN is providing a solution to an unmet medical need in these countries.

Overall, these data confirm the international reach and impact of ESDN and demonstrate how this network approach has transformed the diagnosis of genetic bone diseases worldwide.

5. Sources to corroborate the impact

A. Regional Genetic Laboratory (Manchester, UK) listed on NHS UK Genetic Testing Network (UKGTN): http://ukgtn.nhs.uk/find-a-test/search-by-laboratory/laboratory/manchester-rgc-36/. Homepage: www.ukgtn.nhs.uk. *UKGTN provides a search tool for genetic testing services across the UK*.

B. ORPHANET, www.orpha.net. *The European portal for rare disease and orphan drugs, receiving 12,000 daily visits. Lists laboratories performing molecular diagnosis of PSACH and/or MED.*

C. GENETests, www.genetests.org. *A publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers. Lists laboratories performing molecular diagnosis of PSACH and/or MED.*

D. Email to verify the number of patients tested at GeneDx, Gaithersburg, USA.

E. Email to verify the number of patients tested at Seoul National University Hospital, Korea.

F. Email to verify the number of patients tested at Regional Genetics Laboratory, Manchester, UK.

G. EU Committee of Experts on Rare Diseases (EUCERD) report May 2011: http://ec.europa.eu/health/rare_diseases/docs/eucerd2011_report_european_ref_net.pdf

H. ESDN Case Manager, www.esdn.org/eug/Home and Excel spreadsheets of data analysis.