Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Clinical and genetic characterisation of inherited forms of heart muscle disease and the impact on service provision and patient care

1. Summary of the impact

Over the past decade our research findings have impacted on the diagnosis and treatment of patients with inherited cardiomyopathies. Our work on risk stratification in patients with hypertrophic cardiomyopathy forms the basis for international guidelines on the use of implantable cardioverter defibrillators. Our research in patients with arrhythmogenic right ventricular cardiomyopathy has led to the development of a new international standard for the diagnosis of disease in patients and relatives. We have contributed to national and European guidelines on genetic testing in these conditions. We have also been influential in changing national policies, service design, and provision of care for inherited heart muscle disease.

2. Underpinning research

Cardiomyopathies are primary diseases of the heart muscle, which are usually inherited. They cause a variety of clinical syndromes, including sudden death in apparently healthy young people, heart rhythm disturbances in later life, many of which are fatal, and debilitating heart failure that reduces the quality of life and causes premature death for many patients.

The research reported below represents basic molecular and clinical research undertaken by our group that has had a significant impact on the identification and treatment of patients with cardiomyopathies. It has also underpinned development of the largest inherited cardiovascular disease service in the UK at UCL Hospitals NHS Foundation Trust and Great Ormond Street Hospital. Our research encompasses gene discovery and prevalence, clinical manifestations of disease and prognosis. Our work has resulted in the identification of new disease-causing genes in each of the major subtypes of heart muscle disease, and in rarer conditions; examples are given below.

Hypertrophic cardiomyopathy (HCM): About 1 in 500 of the UK population has hypertrophic cardiomyopathy (HCM), which is the commonest inherited cardiac disease. We have identified new mutations in patients with this condition **[1]**, and have established a new method for the classification of genetic variants **[2]**. The data collected through our clinical evaluation programme have been used to develop the first validated sudden death risk prediction tool for patients with HCM. This provides accurate individualised estimates for the probability of sudden cardiac death (SCD) using readily collected clinical data **[3]**. We currently lead a large international consortium (HCM-RISK) that is developing individualised risk scores for other disease-related outcomes.

Arrhythmogenic right ventricular cardiomyopathy (ARVC): ARVC commonly presents with heart rhythm disturbance and sudden cardiac death in young, previously well individuals. In 2005, systematic evaluation of families with ARVC using cardiac magnetic resonance imaging revealed previously unrecognised sub-clinical forms of disease **[4]**. We and other investigators identified new mutations in families with ARVC **[5]**. Through systematic genetic testing and high fidelity clinical characterisation of patients and relatives harbouring disease-causing genetic mutations our studies revealed a high prevalence of multiple genetic mutations in people with ARVC that convey poor prognosis **[6]**.

Malignant ventricular arrhythmias (MVA) in Lamin A/C mutation carriers: Since 2011, work funded by a European Union seventh framework programme performed in collaboration with other European centres (INHERITANCE Consortium) has led to improved characterisation of patients with laminopathies, a group of diseases caused by mutations in the gene coding for a protein called Lamin AC that accounts for 5-8% of unexplained heart failure and also leads to sudden cardiac death **[7]**.

3. References to the research

[1] Murphy RT, Mogensen J, McGarry K, Bahl A, Evans A, Osman E, Syrris P, Gorman G, Farrell M, Holton JL, Hanna MG, Hughes S, Elliott PM, Macrae CA, McKenna WJ. Adenosine monophosphate-activated protein kinase disease mimicks hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome: natural history. J Am Coll Cardiol. 2005 Mar 15;45(6):922-30. http://dx.doi.org/10.1016/j.jacc.2004.11.053

[2] Lopes LR, Zekavati A, Syrris P, Hubank M, Giambartolomei C, Dalageorgou C, Jenkins S, McKenna W; Uk10k Consortium, Plagnol V, Elliott PM. Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing. J Med Genet. 2013 Apr;50(4):228-39. http://dx.doi.org/10.1136/jmedgenet-2012-101270.

[3] O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; for the Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). Eur Heart J. 2013 Oct 14. http://dx.doi.org/10.1093/eurheartj/eht439

[4] Norman M, Simpson M, Mogensen J, Shaw A, Hughes S, Syrris P, Sen-Chowdhry S, Rowland E, Crosby A, McKenna WJ. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. Circulation. 2005 Aug 2;112(5):636-42. http://circ.ahajournals.org/content/112/5/636.abstract

[5] Syrris P, Ward D, Evans A, Asimaki A, Gandjbakhch E, Sen-Chowdhry S, McKenna WJ. Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocollin-2. Am J Hum Genet. 2006 Nov;79(5):978-84. http://dx.doi.org/10.1086/509122

[6] Quarta G, Muir A, Pantazis A, Syrris P, Gehmlich K, Garcia-Pavia P, Ward D, Sen-Chowdhry S, Elliott PM, McKenna WJ. Familial Evaluation in Arrhythmogenic Right Ventricular Cardiomyopathy: Impact of Genetics and Revised Task Force Criteria. Circulation. 2011 Jun 14;123(23):2701-9. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.976936

[7] van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, van den Berg MP, Pilotto A, Pasotti M, Jenkins S, Rowland C, Aslam U, Wilde AA, Perrot A, Pankuweit S, Zwinderman AH, Charron P, Pinto YM. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. J Am Coll Cardiol. 2012 Jan 31;59(5):493-500. http://dx.doi.org/10.1016/j.jacc.2011.08.078.

4. Details of the impact

Genes identified by our research are now regularly tested for in the UK and around the world. The UCL Hospital (UCLH) inherited disease service is the largest of its kind in the UK, seeing more than 20% of the national caseload. Between 2008 and 2013, a total of 745 patients with cardiomyopathy underwent diagnostic genetic testing at our genetic clinic **[a]**. The benefits to patients are: more accurate description of prognosis; diagnosis in family members; and, if needed, prevention of sudden death through the implantation of defibrillator devices (implantable cardioverter defibrillators, ICD). Genetic testing has also been shown to be highly cost-effective in patients with cardiomyopathy **[b]**.

We have worked with expert groups to produce international guidelines for genetic testing. In 2008, Elliott co-chaired the statement development group (of which McKenna was also a member), which produced an HRUK position statement on clinical indications for genetic testing in familial sudden cardiac death syndromes **[c]**. In 2010, we contributed to guidelines issued by the European Society of Cardiology on genetic counselling and testing in cardiomyopathies **[d]**. These referenced our work in relation to predictive diagnosis in asymptomatic relatives, and recommended screening for genes we had identified. In 2011, McKenna co-authored a consensus statement from the Heart Rhythm Society (HRS) and European Heart Rhythm Association (EHRA) on genetic testing for the channelopathies and cardiomyopathies **[e]**. Work from the group was heavily referenced in this document.

AVRC: Genetic testing of families with ARVC is particularly important. Early disease manifestations may be missed using conventional imaging protocols although individuals remain at risk of sudden cardiac death. Our detailed work examining the relationship between genetic mutations and clinical presentation has led to a new European classification for cardiomyopathies and a clinically-based approach to diagnosis that emphasises disease specific presentations and outcomes, which was outlined in position statements from the European Society of Cardiology in 2008 and 2013 (to which Elliott contributed) **[f]**. Our work studying the expression of genetic mutations in ARVC directly informed the development of new diagnostic criteria for the disease that have resulted in improved detection of disease **[g]**.

HCM: The risk stratification algorithms we developed for HCM have been used to guide ICD implantation. Since 2008, 395 patients with HCM have undergone ICD implantation using the risk tools developed by our group **[a]**. The benefit to patients is prevention of sudden cardiac death, as the device senses a heart rhythm disturbance and can restore normal rhythm. In 2010, these algorithms were incorporated into a position statement issued by the specialist society, Heart Rhythm UK, on clinical indications for ICDs in adult patients with familial sudden cardiac death syndromes **[h]**. Our group is also leading a large European cohort study that aims to construct clinical tools for estimating individual patients' risk for disease-related complications **[i]**. The first risk model was published in October 2013, and will be included in new European treatment guidelines due for publication in 2014.

Lamin AC gene mutations: Our work in patients with heart muscle disease caused by Lamin AC gene mutations showed that most people who inherit the gene develop disease with a predictable natural history beginning with atrial rhythm disturbance in early adulthood with subsequent progression to heart block, potentially fatal ventricular problems and finally to progressive heart failure. Early recognition of these characteristic stages of disease facilitates much earlier diagnosis for patients and families and has allowed us to develop predictive models that identify patients who might benefit from early treatment with anticoagulants and prophylactic ICD implantation. Based on our research, new European Society of Cardiology guidelines for cardiac pacing include a recommendation for ICD implantation in patients with Lamin AC mutations. Since 2008, 22 families with definite Lamin AC mutations have been identified in the UCL screening clinic **[a]**.

Improvement of cardiac services: Throughout the course of our research, we have engaged with policy-makers and specialist organisations to translate our findings into better policy, service design and commissioning of specialist services for these conditions. In 2005, McKenna co-chaired the consultation process of the UK National Service Framework (NSF) on Arrhythmia and Sudden Death, leading to the publication of a new chapter (Chapter 8) of this framework. Building on the work being done at the UCL clinic at the time, this document recommended that evaluation of families should take place in a dedicated clinic with staff who are trained in diagnosis, management and support and with genetic counselling and further testing available if appropriate. McKenna subsequently produced a *Proposal for the Establishment of Inherited Cardiovascular Conditions Centres* which was endorsed by the Department of Health (DH) and, according to the PHG Foundation in 2009, was "*Described as a 'blueprint' for services and quoted many times in DH meetings*" **[j]**. These recommendations have remained key elements of the NHS England commissioning framework for specialist commissioning of inherited cardiovascular disease services that has set out the framework for screening clinics **[k]**.

Work with patient groups: We have also worked closely with patient groups on multiple public and patient engagement initiatives. McKenna and Elliott have both been key speakers at patient days organised by the Cardiomyopathy Association, and McKenna also wrote a review of cardiomyopathy for this charity **[l]**. McKenna is a patron of the charity Cardiac Risk in the Young, and has assisted this organisation with screening for hereditary cardiac diseases **[m]**. McKenna and Elliott are both on the board of advisors for the Hypertrophic Cardiomyopathy Association. McKenna's research is directly cited on the website of this organisation, and he was worked with them, for example, to deliver professional education days highlighting the risks of sudden death due to HCM in young athletes **[n]**.

5. Sources to corroborate the impact

[a] Patient numbers can be corroborated by the Service Manager, Inherited Cardiovascular Disease, the Heart Hospital. Contact details provided.

[b] Wordsworth S, Leal J, Blair E, et al. **DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model.** Eur Heart J. 2010 Apr;31(8):926-35 http://doi.org/bm45tm *References 3 papers from our group.*

[c] Garratt CJ, Elliott PM, Behr E, et al. **Clinical Indications for Genetic Testing in Familial Sudden Cardiac Death Syndromes**: an HRUK Position Statement. *Heart* 2008;94(4):502-7. http://doi.org/d97dvx

[d] Charron P, Arad M, Arbustini E, et al.; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. **Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology** Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2010 Nov;31(22):2715-26. http://doi.org/b9hkdg *References to work on p.2716 [Ref 4] and p.2719 [Ref 24]. See also Table 2, p.2721; Table 5, p.2724*

[e] Ackerman MJ, Priori SG, Willems S, et al.; Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). **HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies**: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011 Aug;13(8):1077-109. http://doi.org/cbg98h *See Section 8, p.1092 and subsequent sections*

[f] 2008 position statement: Elliott P, Andersson B, Arbustini E, et al. **Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology** Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008 Jan;29(2):270-6. (Elliott PM from the UCL group is 1st author)
2013 position statement: Rapezzi C, Arbustini E, Caforio AL, et al. **Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC** Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013 May;34(19):1448-58. (Elliott PM. From the UCL Group is corresponding author. See p1457 [Ref 76])

[g] Marcus FI, McKenna WJ, Sherrill D, et al. **Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria**. Circulation. 2010 Apr 6;121(13):1533-41. (see p1534 [Ref 17 and Ref 29]

[h] Garratt CJ, Elliott P, Behr E, et al.; Heart Rhythm UK Familial Sudden Cardiac Death Syndromes Statement Development Group. **Heart Rhythm UK position statement on clinical indications for implantable cardioverter defibrillators in adult patients with familial sudden cardiac death syndromes**. Europace. 2010;12(8):1156-75. (see p1164 [Ref 76] and 1165 [Ref 81]

[i] www.HCMRisk.org *5 references to work of the UCL group on this page of the website*.

[j] Burton H, Alberg C, Stewart A. Heart to Heart: inherited cardiovascular conditions services – full report. PHG Foundation, 2009: http://www.phgfoundation.org/file/4667 *See p.24*.

[k] http://www.england.nhs.uk/resources/spec-comm-resources/npc-crg/group-a/a09/

[l] Patient days (Feb-Nov 2013). McKenna and Elliot are key speakers:
http://www.cardiomyopathy.org/Info-days.html
Clinical review, by McKenna: http://www.cardiomyopathy.org/Cardiomyopathy-review.html

[m] http://www.c-r-y.org.uk/patrons.htm. Examples of work with the charity: http://www.c-r-y.org.uk/John_sisters.htm and http://www.c-r-y.org.uk/harley_diary.htm.

[n] https://www.4hcm.org/hcma-the-organization/archives/56696-athletes-heart-sudden-death-hypertrophic-cardiomyopathy-a-professional-meeting-stanford.html