PRESS RELEASE

17 August 2016

Improved analysis of genetic testing could lead to more patients with inherited conditions being successfully diagnosed

A groundbreaking study, led by experts from Royal Brompton Hospital and the University of Oxford, has discovered better methods to interpret the significance of gene mutations in patients who are tested for genetic conditions. The findings mean that, in future, more diagnoses could be made through genetic testing.

Researchers compared genetic data from nearly 8,000 patients who have the heart condition cardiomyopathy, with more than 60,000 reference samples from the general population. The aim was to reassess the role that variants in different genes play in causing the condition, which is a disease of the heart muscle that reduces its ability to pump blood around the body.

The cardiomyopathy data set, from the Oxford Molecular Genetics Laboratory and the Laboratory of Molecular Medicine, Partners HealthCare in Boston, USA, is the biggest ever analysed. Researchers compared this with a large volume of raw genetic data from the general population, available from a new database known as ExAC, which was compiled by an international consortium led by the MacArthur Lab in the USA.

Rare variants in genes that are typically associated with dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), were examined.

The results, published today in the journal *Genetics in Medicine*, found that rare variants in some of these genes were not any more common in the cardiomyopathy patients than the general population. This shows they are unlikely to be valid disease-causing genes and that having rare gene variants is collectively more common than previously thought.

The analysis found that only eight out of 48 genes previously implicated in DCM, and two thirds of genes that are regularly screened for HCM, were found to be much more common among the cardiomyopathy patients. This means they are more likely to be disease-causing and therefore most relevant for genetic testing. As a result, clinical scientists can take a more targeted approach and have increased confidence to provide a positive diagnosis if one of these gene variants is found. In the past clinical labs may have taken a more conservative approach, meaning that patients might have received an inconclusive result.

Cardiomyopathies are diseases of the heart muscle, which affect around 1 in 500 people in the UK. The condition causes the heart to stop pumping blood as efficiently as it should, which can lead to heart failure or an irregular heartbeat. Symptoms include breathlessness, chest pain, palpitations, dizziness and loss of consciousness. Cardiomyopathies are the most common cause of sudden death in otherwise healthy young people.

Relatives of cardiomyopathy patients often undergo heart tests because the condition can be genetic. Those found to have no symptoms may have a genetic test to confirm they have the same gene variant as their family member, meaning they can be monitored and treated, often before the condition can be detected on conventional tests. Those who do not have the faulty gene can be reassured and avoid long-term follow-up, saving the NHS money. Currently, if genetic testing is inconclusive, relatives usually receive life-long care in case they later develop the condition. It is hoped the new research findings will lead to an increase in the number of conclusive diagnoses.

Researcher Roddy Walsh, from the NIHR Royal Brompton Cardiovascular Biomedical Research Unit, is a lead author of the paper. He said:

> “This study has major implications for other diseases with strong genetic components as researchers can apply the same techniques to other studies using the ExAC database. The huge reference data set gives us an unprecedented understanding of gene variation in a normal population, while the large collection of data from cardiomyopathy patients has allowed us to make new insights into the disease.

> "Overall, the database has found higher levels of gene variants in the general population than previously thought, but many of these do not cause disease. So it is about knowing what is significant and what isn't, and communicating that to clinicians so they know how best to interpret genetic tests."

BHF Professor Hugh Watkins, director of the BHF Centre of Research Excellence and head of the Radcliffe Department of Medicine at the University of Oxford, and one of the senior authors of the paper, said:

> "These results will help diagnostic laboratories avoid testing genes that can't be interpreted reliably and be more confident in interpreting variants in the genes that we have shown to be valid."

Professor Stuart Cook, director of genetics at Royal Brompton & Harefield NHS Foundation Trust and Tanoto Foundation professor of cardiovascular medicine at the SingHealth Duke-NUS Academic Medical Centre in Singapore, is another senior author. He said:

> "For the first time, we can really look at what is important and what is not. This helps us pinpoint the variants that are causing the disease and identify parts of protein that are hotspots for the mutations. When we can be firmer in our diagnosis we no longer have to carry out follow-up tests for those who don't need it, which saves money."

The research was supported by the NIHR Royal Brompton Cardiovascular Biomedical Research Unit and Imperial College London, NIHR Oxford Biomedical Research Centre, the British Heart Foundation, Wellcome Trust, Fondation Leducq, Medical Research Council, Academy of Medical Sciences and National Medical Research Council (NMRC) Singapore.

- ends -

For further information, please contact:

Cara Lee
Media relations officer
Royal Brompton & Harefield NHS Foundation Trust
Tel: 020 7352 8121 ext 2237
Mobile: 07891 310 924
Email: c.lee3@rbht.nhs.uk
Follow us on Twitter: @RBandH

Notes to editors:

1. **Royal Brompton & Harefield NHS Foundation Trust** is the UK's largest specialist centre for the treatment of heart and lung disease. Working from two sites, Royal Brompton Hospital in Chelsea, West London, and Harefield Hospital, near Uxbridge, the Trust has an international reputation for the expertise of its staff, high standard of care and research success. Experts at the Trust help patients from all age groups who have heart and lung problems and provide some of the most complex surgery and sophisticated treatments available anywhere in the world.

   The Trust is the UK's largest centre for the treatment of adult congenital heart disease and is the country's leading provider of specialist respiratory care. Over the years the Trust has been responsible for major medical breakthroughs, such as the UK's first combined heart and lung transplant. It established the UK's first adult service for cystic fibrosis, which is now one of Europe's biggest treatment centres for the condition, and has pioneered the use of primary angioplasty for the treatment of heart attacks. Today the Heart Attack Centre at Harefield has one of the fastest arrival-to-treatment times in the UK, a crucial factor in patients' survival.

   As a member of the Academic Health Science Centre (AHSC), in collaboration with Imperial College London, Imperial College Healthcare Trust and The Royal Marsden NHS Foundation Trust, the Trust helps to drive innovation and improved care for over 1.1 million patients each year in North West London, by aligning the research, education and clinical services of the partner organisations. For further information, visit www.rbht.nhs.uk

2. Consistently rated amongst the world's best universities, **Imperial College London** is a science-based institution with a reputation for excellence in teaching and research that attracts 14,000 students and 6,000 staff of the highest international quality. Innovative research at the College explores the interface between science, medicine, engineering and business, delivering practical solutions that improve quality of life and the environment - underpinned by a dynamic enterprise culture.

3. **The University of Oxford's Medical Sciences Division** is one of the largest biomedical research centres in Europe, with over 2,500 people involved in research and more than 2,800 students. The University is rated the best in the world for medicine, and it is home to the UK's top-ranked medical school. From the genetic and molecular basis of disease to the latest advances in neuroscience, Oxford is at the forefront of medical research. It has one of the largest clinical trial portfolios in the UK and great expertise in taking discoveries from the lab into the clinic. Partnerships with the local NHS Trusts enable patients to benefit from close links between medical research and healthcare delivery. A great strength of Oxford medicine is its long-standing network of clinical research units in Asia and Africa, enabling world-leading research on the most pressing global health challenges such as malaria, TB, HIV/AIDS and flu. Oxford is also renowned for its large-scale studies which examine the role of factors such as smoking, alcohol and diet on cancer, heart disease and other conditions.

4. **The NIHR Oxford Biomedical Research Centre** is funded by the National Institute for Health Research, and is a partnership between the Oxford University Hospitals NHS Foundation Trust and the University of Oxford. The NIHR provides the NHS with the support and infrastructure it needs to conduct first-class research funded by the Government and its partners alongside high-quality patient care, education and training. Its aim is to support outstanding individuals (both leaders and collaborators), working in world class facilities (both NHS and university), and conducting leading edge research focused on the needs of patients.

5. The **National Institute for Health Research (NIHR)** is funded by the Department of Health to improve the health and wealth of the nation through research. The NIHR is the research arm of the NHS. Since its establishment in April 2006, the NIHR has transformed research in the NHS. It has increased the volume of applied health

research for the benefit of patients and the public, driven faster translation of basic science discoveries into tangible benefits for patients and the economy, and developed and supported the people who conduct and contribute to applied health research. The NIHR plays a key role in the Government's strategy for economic growth, attracting investment by the life-sciences industries through its world-class infrastructure for health research. Together, the NIHR people, programmes, centres of excellence and systems represent the most integrated health research system in the world. For further information, visit the NIHR website (www.nihr.ac.uk).