MedicalXpress

Scientists publish first complete record of genetic mutations behind rare vascular disease

September 25 2015

The genetic architecture of a debilitating and potentially fatal vascular disease has for the first time been detailed in its entirety, providing clinicians with the comprehensive data needed to improve diagnosis and deliver more personalised patient care.

Scientists investigating Pulmonary Arterial Hypertension (PAH) have compiled the most up to date and complete record of all the defective variations found in the genes that cause the disease.

The new study, led by Dr Rajiv Machado from the University of Lincoln, UK, draws together the complete genetic information of hundreds of individuals affected by PAH. This advance will not only offer new opportunities to identify the mutation which causes PAH in individual patients but will also provide an important tool to correlate genetic data, allowing for more tailored approaches to the clinical management of the disease. It has been published in the online academic journal *Human Mutation*.

PAH is an often fatal disorder resulting from several causes, including an assortment of genetic defects. It is a progressive disease characterised by abnormally high blood pressure (hypertension) in the pulmonary artery, the blood vessel that carries blood from the heart to the lungs. Symptoms are shortness of breath, dizziness, swelling (oedema) of the ankles or legs, chest pain and a racing pulse.

Heritable PAH leads to a chronic elevation of pulmonary arterial pressure, which can result in heart failure.

While mutations in a gene called BMPR2 are the single most common cause for hereditary cases, mutations capable of causing disease have been observed in approximately 25 per cent of patients without a prior family history of disease.

The new study, which brings together data from specialist PAH centres based in Germany, France, North America and the UK, describes molecular genetic analyses of the 10 functionally characterised genes that cause PAH and provides a compilation of all mutations identified to date.

It also describes an additional 370 independent mutations of BMPR2 in patients, either previously excluded from or identified since the last comprehensive mutation update by Dr Machado and colleagues in 2009. Of these, 81 are new variations.

Dr Machado, from the University of Lincoln's School of Life Sciences, said: "This is the most comprehensive and complete compilation of all defective variations in the genetic risk factors for PAH. This will allow the clinical geneticists, with a greater degree of certainty, to conclude that the gene variations present in a patient are either disease causing or of unknown significance. This could inform a patient's decisions about starting a family or undertaking pre-natal testing. Prior to this a clinician would have to try and understand genetic data received for a single patient by trawling through historic manuscripts to make a diagnosis. This report has the potential to be of great importance to the diagnostic centres around the world.

"The continuing identification of genetic factors, as explored in this paper, provides unique insight to the genetic mechanisms driving

disorders of pulmonary vascular function. These data provide a key resource in data interpretation and how these genetic insights may lead to the potential discovery and delivery of novel targeted therapeutic options in PAH."

This important resource of clinical and scientific data has now been posted on a freely available public repository, namely ClinVar, and will be accessible through Dr Machado's Lincoln profile page.

The emergence of next-generation sequencing (NGS) allows scientists to sequence much more quickly and cheaply, and as such has revolutionised the study of genomics and molecular biology. NGS has allowed researchers to identify novel, rare genetic variations in the PAH disease spectrum, detailed in this study. It is likely that future avenues will include the use of more NGS technologies, the pinnacle of which is whole-genome sequencing - a process that determines the complete DNA sequence of an organism's genome at a single time.

More information: "Pulmonary Arterial Hypertension: A current perspective on established and emerging molecular genetic defects." DOI: 10.1002/humu.22904

Provided by University of Lincoln