Anglo-French team discover elusive gene that makes platelets gray

July 25 2011

Researchers have identified an elusive gene responsible for Gray Platelet Syndrome, an extremely rare blood disorder in which only about 50 known cases have been reported. As a result, it is hoped that future cases will be easier to diagnose with a DNA test.

The findings were made following a collaborative study by Professor Willem Ouwehand and Dr Cornelis Albers, who are both based at the Wellcome Trust Sanger Institute and the University of Cambridge, and Dr Paquita Nurden, from the Rare Platelet Disorders laboratory, based in Bordeaux, who have described how they achieved this.

Platelets are the second most abundant cell in the blood. Their main task is to survey the blood vessel wall for damage and to orchestrate its repair where required. On the flip side, platelets also play a "darker" role after vessel wall damage and cause blood clots that may lead to heart attacks or stroke.

Some people are born with platelets that do not function well and these rare conditions are thought to be inherited. Gray Platelet Syndrome poses a risk of bleeds, some of which can be severe and life threatening, e.g. if they occur in the brain. Gray Platelet Syndrome was first identified in the 1970s and is named for the grayish appearance of these platelets when viewed with a microscope.

Identifying the cause of increased bleeding in young patients has been a painstaking process. An important step in translating research findings in

human genetics in improvements of patient care has focused around the need to develop simpler and rapid DNA-based diagnostic test. To achieve this, researchers needed to discover the gene responsible for the rare platelet bleeding disorders.

In the past it was a major challenge to discover which genes caused rare disorders because DNA samples from numerous large families affected by the same disorder had to be identified and genetically analysed to pinpoint the region harbouring the causative gene.

To achieve their latest findings, researchers used a simpler approach and deciphered about 40 million letters of genetic code covering the entire coding fraction of the genome of four non-related French patients.

They identified the gene NBEAL2 as not functioning well in Gray Platelet Syndrome, a member of a family of genes that all contain a unique domain, called the BEACH domain. The team showed that protein encoded by this gene is altered at a different position in the four non-related cases and the patients affected by the disorder have inherited two non-functioning copies of the gene, one from father and mother each.

"It is really great to see how the use of modern genomics technologies is going to be of direct benefit for patient care. It is exciting that we have shown that the genetic basis of a rare bleeding disorders can be discovered with relative ease", said Professor Willem Ouwehand, who heads a NHS Blood and Transplant research team on platelet biology at both the Wellcome Trust Sanger Institute and the University of Cambridge. "This study is one such example and it gives us confidence to achieve the same for a large number of other rare inherited platelet bleeding disorders. It is now important that we use this discovery to improve patient care in the NHS and beyond."

The team's identification of the NBEAL2 gene was confirmed by functional studies in zebrafish. Fish also have platelets named thrombocytes, and switching off the NBEAL2 gene in fish caused a complete absence of these cells which resulted in nearly half of the fish suffering spontaneous bleeds similar to patients with the disorder.

It is hoped that this gene identification will make it simpler to diagnose future cases of Gray Platelet Syndrome with a simple DNA test. This new test is now being developed with researchers at the NHS Blood and Transplant Centre at the Addenbrooke's Biomedical campus in Cambridge as part of the international ThromboGenomics initiative.

The scientists observed that other members from the same family of BEACH proteins are implicated in other rare inherited disorders. Their findings showed that LYST protein did not function well in Chediak-Higashi syndrome, another rare but severe disorder paralysing the immune system but also causing a mild platelet bleeding disorder. As a result, a picture is emerging that BEACH proteins are essential in the way granules in blood cells and brain cells are formed or retained showing that in platelets the BEACH proteins are essential for both alpha and dense granules.

"Our discovery that another member of the family of BEACH proteins is underlying a rare but severe granule disorder in platelets firmly nails down the important role of this class of proteins in granule biology," said Cornelis Albers, a British Heart Foundation research fellow at the Sanger Institute and the University of Cambridge. "The reasons why the platelets of patients with Gray Platelet Syndrome are gray is because they lack alpha granules. The alpha granules carry the cargo of proteins that induce vessel wall repair and also form the platelet plug.

"A better understanding of how these granules are formed and how their timely release by the platelet is coordinated at the molecular level may

one day underpin the development of a new class of safer anti-platelet drugs for use in patients with heart attacks and stroke. It has been a fascinating journey to identify a new and important pathway by combining the rapid advances in sequencing technology with computational analysis."

The French collaboration was led by Dr Paquita Nurden who set up the Network for Rare Platelet Disorders at the Laboratoire d'Hématologie, Hopital Xavier Arnozan close to Bordeaux. Their team made the Heruclian effort to find the French families affected by this rare disorder.

"We have worked for years to identify the families across France that suffer from rare platelet disorders and my group of scientists have used powerful microscopes to determine what was wrong with the platelets from patients with Gray Platelet Syndrome. We discovered in the 1980s that something was wrong with the alpha granules because they were lacking in most of the cases," said Dr Nurden, an international expert in platelet biology. "The gene, however, remained elusive for another 30 years, and it is great how our joint working has discovered the causative gene very quickly."

Provided by Wellcome Trust Sanger Institute

Citation: Anglo-French team discover elusive gene that makes platelets gray (2011, July 25) retrieved 25 April 2024 from https://medicalxpress.com/news/2011-07-anglo-french-team-elusive-gene-platelets.html