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Study tracks worldwide spread of beneficial blood cell gene variant

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Two beneficial variants of a gene controlling red blood cell development have spread from Africa into nearly all human populations across the globe, according to a new study led by King's College London. The international team studied the genomes of world populations to look for the origin of changes in a key regulator gene which stimulate fetal haemoglobin production into adulthood. Fetal haemoglobin is normally found in fetuses and infants, but some patients with inherited blood disorders who are able to keep making it as adults experience milder symptoms of their condition.

Sickle cell anaemia is an inherited blood disorder in which red blood cells behave abnormally and can clog blood vessels, leading to acute unpredictable painful spells called a sickle cell crisis which typically last a week. The recurrent sickle crises and chronic anaemia lead to serious complications in the joints, bones, lungs, eyes, brain, liver and kidneys, and early death. Thalassaemia is a group of inherited blood disorders where insufficient haemoglobin - the oxygen-carrier in blood cells - is produced, leading to anaemia. Symptoms of beta thalassaemia can range from moderate to severe, with the most severe form requiring blood transfusions for the rest of the person's life. The only 'cure' for both sickle cell anaemia and beta thalassaemia is a bone marrow transplant, but this option is only available to a small number of patients.

Studies have shown that carriers of these conditions are protected against malaria; having one copy of the sickle cell gene significantly increases your chances of surviving malaria. As a result, these blood disorders are

more prevalent in parts of the world where malaria is common. However, sickle cell disease is rapidly emerging as a public health issue both globally and in the UK where it is the most common severe genetic disorder, affecting an estimated 13,000 people.

The new study, published in the *Annals of Human Genetics*, looked at genetic factors that can reduce the severity of these blood disorders. Typically, our bodies make fetal haemoglobin whilst in the womb, but then switch to another form of haemoglobin, adult haemoglobin, at birth. However, we continue to produce very small amounts of fetal haemoglobin in adulthood, some more than others. Patients who have the genetic factors that increase fetal haemoglobin production tend to have milder symptoms of their blood disorder.

While studying patients of African and of South Asian descent, the authors noticed that one such factor, a genetic variant controlling the red blood cell regulator gene MYB - 'MYB enhancer variant' - on Chromosome 6, is of similar genetic structure not only in both patient groups, but also in healthy individuals, including those of Northern European origin, where thalassaemia and sickle cell disease are rare. This led the authors to suspect that beneficial MYB enhancer variants, which promote fetal haemoglobin in the body, are a general feature of human populations across the world and that they might have a common origin.

To test this hypothesis, the team searched for genetic signatures of such variants in public genome data generated from world populations to see whether they existed in other ethnic groups. They found signatures for two different types of MYB enhancer variants, HMIP-2A and HMIP-B, in major human population groups and in nearly all ethnic groups covered by the data. Both variants occur in Sub-Saharan Africa, but only at low frequencies. In much of the rest of the world the alleles have combined, forming HMIP-2A-B, and this combination is relatively

common in Europe, South Asia and China. HMIP-2B separately is common in Far-East Asian peoples and in Amerindians, illustrating their connection across the Bering Strait.

The team also tested recent genome sequence data from our extinct cousins, the Neanderthals and Denisovans, and from the Great Apes, but detected neither HMIP-2A nor HMIP-2B. From this, the authors conclude that MYB enhancer variants that modulate the severity of sickle cell and beta thalassaemia have arisen twice in modern humans, in Africa, and then spread to the rest of the world. However, this likely occurred long before inherited blood disorders became prevalent, and thus the environmental factors that favoured such variants in these early humans are not clear.

The next stage of the research will explore which selection pressures or benefits might have contributed to the present population distribution of the variants. Selection pressures could include nutritional factors, such as the availability of iron in the diet, or specific demands on red blood cell production, such as adaptation to high altitudes.

Dr Stephen Menzel, co-author from the Department of Molecular Haematology at King's College London, says: "Patients who have milder versions of blood disorders, thanks to their ability to keep producing fetal haemoglobin, carry genetic clues that are helping us to understand the function of the genes and biological pathways involved in these diseases."

Professor Swee Lay Thein, co-author and Consultant Haematologist at King's College Hospital NHS Foundation Trust, says: "King's Health Partners cares for the largest cohort of sickle cell patients in the UK, with an estimated 2,500 patients. Although a newborn in the UK can now expect to live to adulthood, in adults the disorder has evolved into a chronic debilitating disease with acute or chronic pain and organ

complications. We hope our research will help to develop biomarkers and ultimately, preventative treatments for inherited blood disorders."

Provided by King's College London