Researchers discover a rare new blood group system

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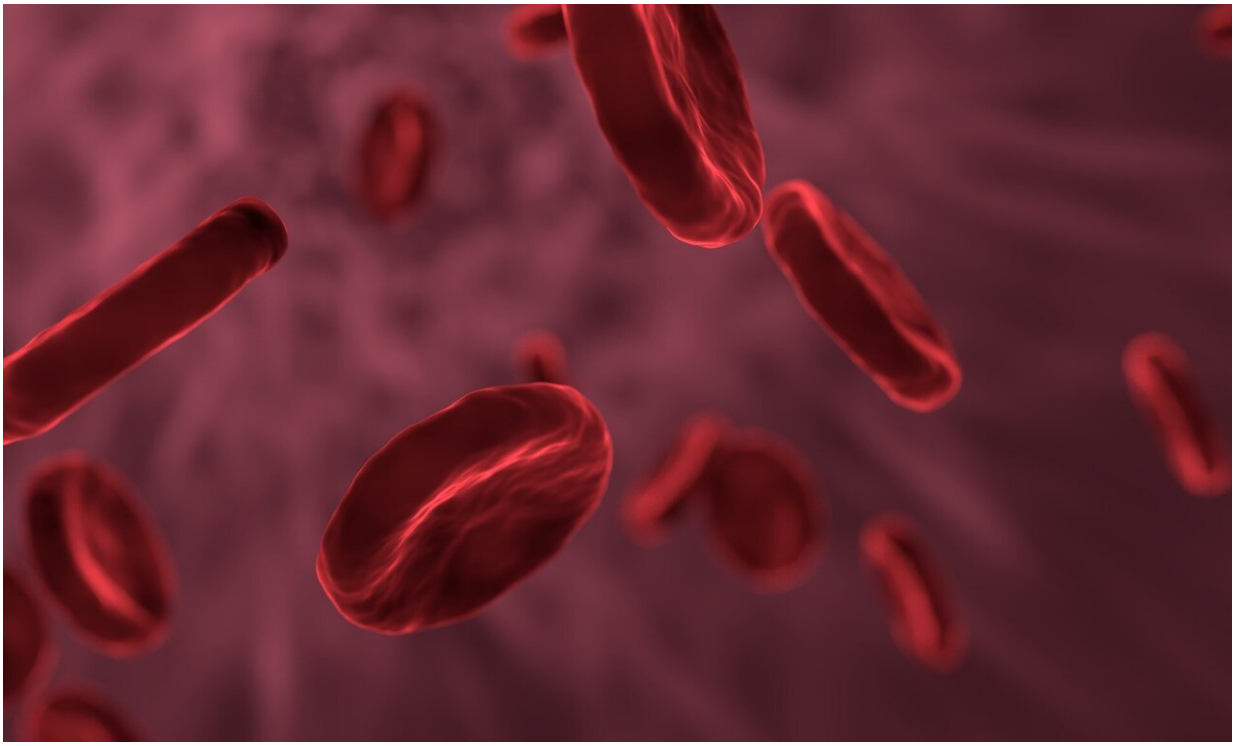

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Scientists from the University of Bristol and NHS Blood & Transplant (NHSBT) have discovered a rare new blood group system. The findings, published in *Blood*, also solve a 30-year mystery.

A person's blood type is determined by the presence or absence of

proteins known as blood groups that are present on the surface of red blood cells. Although most people are familiar with the concept of blood groups such as ABO or Rh (the plus or minus), there are many other important blood groups. Where mismatch exists between one person's blood and that of another, the possibility of alloimmunization (the process by which a person generates an antibody against a blood group antigen that they do not carry) arises. The presence of alloantibodies can have clinical consequences in transfusion or pregnancy by triggering an attack by the immune system

Researchers from Bristol's School of Biochemistry and NHSBT's International Blood Group Reference Laboratory (IBGRL) spearheaded an international collaboration which sought to investigate a 30-year mystery surrounding the basis of three known, but genetically uncharacterized, antigens that did not fit into any known blood group system.

In this study, individuals with alloantibodies against a collection of antigens termed Er, that were first observed more than 30-years ago, were investigated by applying a powerful technique allowing simultaneous analysis of all their gene coding DNA sequences. Specific changes were identified in the gene coding for the Piezo1 protein, which would result in the production of an altered protein on the cell surface of these individuals. Using gene editing in an immortalized cell-line developed in Bristol, the Piezo1 protein was first removed and then reintroduced to definitively prove that alloantibodies to Er antigens (including two never before reported) bind to Piezo1, and that Piezo1 is required for Er antigen expression.

Using a combination of cutting-edge DNA sequencing and gene-editing techniques, the team were able to conclusively show that Piezo1, a protein of widespread biological interest, is the carrier for these sites (and more) and, in so doing, establish Er as a new blood group system.

Sadly, alloantibodies found in two pregnant women to two newly discovered Er antigens reported in this work were associated with tragic loss of their babies. Discovering the genetic basis of blood groups allows scientists to develop new tests to identify those with uncommon blood groups, with the aim of providing the best possible care for patients with even the rarest of blood types. Piezo1 is known to have important roles in both health and disease and, although there is still much for us to understand, the team's breakthrough further enhances our knowledge and represents another new milestone in blood sciences.

Dr. Tim Satchwell, one of the study's lead authors at the University of Bristol, said, "This study is a great example of how new technologies can combine with more traditional approaches to address long-standing questions that would have been impossible to answer not that many years ago. The fact that Er turned out to be Piezo1, a protein with such widespread interest makes it even more intriguing."

Professor Ash Toye, Professor of Cell Biology at the University of Bristol and Director of the NIHR Blood and Transplant Research Unit, said, "This work demonstrates that even after all the research conducted to date, the simple red blood cell can still surprise us. Piezo proteins are mechanosensory proteins that are used by the red cell to sense when its being squeezed. The protein is present at only a few hundred copies in the membrane of each cell. This study really highlights the potential antigenicity of even very lowly expressed proteins and their relevance for transfusion medicine."

More information: Vanja Karamatic Crew et al, Missense mutations in PIEZO1, encoding the Piezo1 mechanosensor protein, define the Er red blood cell antigens, *Blood* (2022). DOI: 10.1182/blood.2022016504

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