International team discovers new genetic immunodeficiency

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An analysis of five families has revealed a previously unknown genetic immunodeficiency, says an international team led by researchers from Boston Children's Hospital. The condition, linked to mutations in a gene called DOCK2, deactivates many features of the immune system and leaves affected children open to a unique pattern of aggressive, potentially fatal infections early in life.

As the researchers—led by Kerry Dobbs and Luigi Notarangelo, M.D., of Boston Children's Division of Allergy and Immunology—reported today in the *New England Journal of Medicine*, DOCK2 deficiency may be detectable by newborn screening and is curable with a hematopoietic stem cell transplant (HSCT).

Genetic immunodeficiencies, such as X-linked severed combined immunodeficiency (X-SCID) or Wiskott-Aldrich syndrome (WAS), are a group of devastating conditions where mutations to specific genes cause either functional defects in or interfere with production of T-cells and other components of a patient's immune system. These defects increase a patient's susceptibility to a range of severe infections at an early age.

Conditions for which the causative genes are known, such as X-SCID, can be screened for at birth, allowing for early detection and, when appropriate, curative treatment with a hematopoietic stem cell transplant.

'Until recently, a correct diagnosis for babies born with SCID or other combined immunodeficiencies, such as DOCK2 deficiency, could be made only after these babies had developed serious infections, which could lead to death or compromise the efficacy of an HSCT,' said Notarangelo, who is a professor of pediatrics at Harvard Medical School. 'Newborn screening for these diseases is now available for most babies with SCID born in the USA, and this gives increased chances of definitive cure by performing the transplant while the baby is still well.'

In the current study, Notarangelo, Dobbs and their colleagues at the Rockefeller University and the Center for Molecular Medicine in Austria, conducted genetic, genomic and immunological analyses on five patients from Lebanon, Finland, Turkey and Honduras/Nicaragua who early in life demonstrated symptoms indicating a severe but distinctive immunodeficiency, one that left patients susceptible to a broad range of infections but particularly vulnerable to viruses. Three out of the five patients were born of closely related parents, and three were successfully treated by HSCT.

The team discovered through whole exome sequencing that all five patients harbored mutations in DOCK2, mutations that rendered the DOCK2 protein inactive. The mutations had profound effects on multiple aspects of the patients' immune systems, causing a profound decrease in T-cells and defects in T-, B- and natural killer (NK) cell function.

The study data show that defects in DOCK2, which helps immune cells react to external chemical signals, can have a profound effect on several aspects of immunity, including unforeseen affects on how non-immune cells (such as cells of the skin) respond to viruses.

Notarangelo noted that the data expand the field's understanding of the basic molecular mechanisms underlying human immunity, while adding a new diagnostic target for newborn screening.

'Although congenital immunodeficiencies are rare diseases, the study of these disorders has been essential in identifying key mechanisms governing the immune system's development and function, and how it helps fight against infections,' he said. 'The knowledge gained has also allowed development of new drugs that harness the immune system to treat more common conditions,

including tumors and autoimmune diseases.'

Provided by Children's Hospital Boston