Researchers find new genetic cause of severe combined immune deficiency disease

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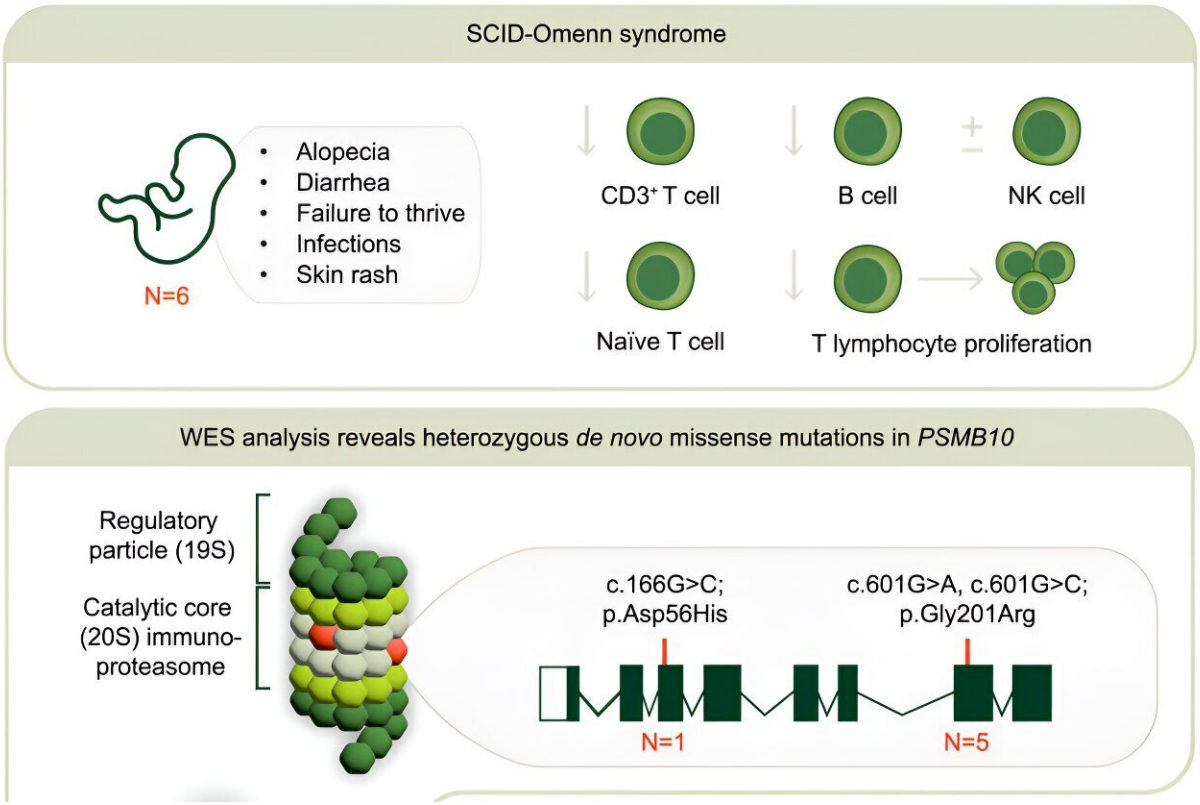

Credit: *The American Journal of Human Genetics* (2024). DOI: 10.1016/j.ajhg.2024.02.013

Researchers from Nijmegen and Newcastle have discovered a new genetic mutation leading to severe combined immune deficiency

disorder (SCID). It's the first time a mutation in the proteasome, a molecular shredder, has been linked to this serious disease.

It is perhaps the most well-known rare disease. A still-young John Travolta (Grease, Pulp Fiction, etc.) plays a teenager growing up with the disease in the movie "The Boy in the Plastic Bubble." Musician Paul Simon references it in his hit song "The Boy in the Bubble," taken from the LP "Graceland." Stories about such individuals captured the attention of the general public in the 1970s, 1980s, crystallized around the dramatic life story of David Vetter.

This interest was not surprising. For Vetter and all the others with the disease, the only way they could stay alive was to be confined in a sterile, small plastic space. At the time, it was the only "treatment" for the disease they were born with. This severe combined immunodeficiency (SCID), as the genetic disorder is officially called, undermines the immune system so severely that even the smallest infections lead to death quite quickly. Therefore, a sterile plastic bulb like a second skin must prevent fungi, viruses or bacteria from entering the body.

After Vetter has been kept in a sterile environment from birth for 12 years, the technique of a bone marrow transplant offers a possible way out. His younger sister donates the bone marrow, and if the transplant succeeds, a new and full-fledged immune system can develop from it, making life in the sphere no longer necessary. But it all turns out differently, as can be read in "Bursting the Bubble: The Tortured Life and Untimely Death of David Vetter" published in 2019 and written by Vetter's psychologist Mary Murphy.

SCID is a collection of inherited, congenital abnormalities of the immune system. The problem arises from mutations in genes that play an important role in the production and function of B and T cells. Without those cells, recognizing and clearing bacteria, viruses and other invaders

is not possible. That is precisely what makes it a life-threatening disease. The most common form is X-linked SCID, but ADA deficiency, Omenn's syndrome and mutations in the JAK3 and Artemis gene all lead to slightly different forms of SCID. Not all genetic mutations leading to SCID are yet known.

Two remarkable cases

The same was true of the SCID baby referred in 2005 to Radboud UMC, the Netherlands. Even though the genetic mutation couldn't be found, the baby received a stem cell transplant after three months, which ultimately succeeded despite all complications.

Years later, Alexander Hoischen's group, which specialized in detecting inborn immunity disorders, searched again for the mutation. They made two remarkable discoveries. First, they saw that revertant mosaicism had occurred in many of the patient's body cells. Further, they found a genetic mutation in the patient not originating from either father or mother. It arose very early in the child itself, a so-called de novo mutation.

Reversing mutations

Hoischen explains, "In each new generation, dozens of changes in DNA arise spontaneously, usually in parts we think have little effect. But one or two of those mutations take place in genes, with often important consequences. In this patient, we saw a de novo mutation in the PSMB10 gene."

Furthermore, a phenomena called revertant mosaicism had occurred several times during embryonic development.

Hoischen says, "It occurs when a body tries to remove a nasty mutation from its own cells to restore the old state. You could call it a kind of natural gene therapy. Because this only happens for a part of the body's cells, genetically different cell lines are created: in short, mosaicism. Revertant, means that the mutation is reversed. And in which piece of DNA did we see this revertant mosaicism occur? Exactly at the place where we found this de novo mutation. That convinced us we were looking in the right direction."

Six rare patients

Solid evidence calls for replication, for more similar patients. With Cas van der Made and other colleagues, Hoischen searched worldwide for medical geneticists who had patients with a similar mutation.

Through their global network, they soon tracked down a patient in Israel, followed by as many as three patients at Sophie Hambleton's research center in Newcastle, where much genetic research on SCID is done. So all with a mutation in the gene in question. And all with the same specific form of SCID: SCID-Omenn syndrome.

While a scientific paper with the findings was being prepared, a sixth patient was found in Newcastle by newborn genetic screening. After a quick stem cell transplant, the baby survived. So did the Nijmegen patient. The other four patients all received stem cell transplants as well, but eventually died from complications of the disease.

Molecular shredder

The question is what this PSMB10 gene exactly does, and why SCID-Omenn arises when a mutation occurs in it. The gene codes for a protein that gets built into the proteasome, a large protein complex that cuts up

damaged, redundant or dangerous proteins like a kind of molecular shredder.

Hoischen explains, "We already know mutations in other proteins of this proteasome lead to autoinflammatory diseases, such as periodic fevers. It is possible that mutations in PSMB10 lead to improper cutting of proteins from bacteria and other pathogens. This cutting is important because the immune system recognizes, picks up and disposes of invaders based on well-cut, characteristic protein fragments, from well-made molecular photographs you might say.

"Without a good picture, there's no detection. Possibly the proteasome also plays a role in cutting pieces of protein used by the immune system itself. But exactly how it does so requires further research. For now the importance of getting this news out to patients as soon as possible was key."

Finer-grained newborn screening

"This discovery has direct implications for SCID newborn screening, for counseling on stem cell transplants and treatment of severe inflammatory complications," says Stefanie Henriet, a pediatrician involved in this study.

Since 2021, SCID has been in the nationwide newborn screening program, and with success. In a way, the screening yields more than was anticipated. Other serious conditions outside the strict definition of SCID, such as severe T-cell deficiency, were found by the screening.

"The question arises from the professionals involved whether these other diseases being detected should also become a formal part of heel prick screening," the Dutch Health Council (Gezondheidsraad) recently wrote on its website. "This can be done by expanding the current definition of

the target disease. The State Secretary of Health, Welfare and Sport has asked the Health Council to advise on such an expansion. After all, expanding the target disease definition involves an expansion of the current newborn screening."

Hoischen remarks, "Genetic research into rare but serious congenital immune disorders such as our mutual research into this specific form of SCID-Omenn syndrome [is] the source for increasingly fine-grained diagnostics and personalized medicine that is increasingly focused on the individual patient."

More information: Caspar I. van der Made et al, Expanding the PRAAS spectrum: De novo mutations of immunoproteasome subunit β-type 10 in six infants with SCID-Omenn syndrome, *The American Journal of Human Genetics* (2024). DOI: 10.1016/j.ajhg.2024.02.013

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