Scientists have pinpointed genetic changes that can leave children born with little to no immune defense against infection.

In a new study of 11 affected individuals, researchers from Newcastle University, the Wellcome Sanger Institute, the Great North Children's Hospital, and their collaborators were able to link mutations in the
NUDCD3 gene to Severe Combined Immunodeficiency and Omenn syndrome—rare and life-threatening immunodeficiency disorders. These mutations prevented the normal development of diverse immune cells needed to combat different pathogens.

The findings, published in Science Immunology, open opportunities for early diagnosis and intervention for this condition.

Severe Combined Immunodeficiency (SCID) and Omenn syndrome are both rare genetic disorders that leave children without a functional immune system and at risk of life-threatening infections. Without urgent treatment, such as stem cell transplants to replace the faulty immune system, many affected will not survive their first year.

While newborn screening methods can flag T cell deficiency, knowledge of the specific genetic cause increases confidence in the diagnosis of SCID and informs the choice of curative therapy. Currently, this remains out of reach for at least one in 10 affected families.

In this new study, researchers from Newcastle University, the Wellcome Sanger Institute and their collaborators studied 11 children across four families, two of whom had SCID while the other nine had Omenn syndrome. All had inherited mutations that disrupted the function of the NUDCD3 protein, which had not previously been linked to the immune system.

Using detailed studies of patient-derived cells and mouse models, the team demonstrated that NUDCD3 mutations impair a crucial gene-rearranging process called V(D)J recombination, essential for generating the diverse T cell receptors and antibodies needed to recognize and fight different pathogens.

While mice engineered with the same NUDCD3 mutations had milder
immune problems, the human patients faced severe, life-threatening consequences. Two patients did survive, however, after receiving a stem cell transplant—reinforcing the importance of early diagnosis and intervention.

Dr. Gosia Trynka, author of the study at the Wellcome Sanger Institute and science director at Open Targets, said, "For babies born with high-risk immunodeficiencies, early detection can mean the difference between life and death. These diseases leave newborns essentially defenseless against pathogens that most of us can easily fend off. The identification of this new disease gene will help clinicians to make a prompt molecular diagnosis in affected patients, meaning they can receive life-saving treatments more quickly."

Professor Sophie Hambleton, senior author of the study at Newcastle University and practicing pediatric immunologist at the Great North Children's Hospital, said, "SCID and Omenn syndrome are devastating disorders, requiring complex and timely treatments. The more we can understand about its underlying causes, the better we can look after affected babies.

"Our research is aimed at filling in the gaps so that families can achieve a molecular diagnosis while we continue learning more about how the immune system works in health and disease. We are deeply grateful to the families whose invaluable participation in this study will help future generations."
