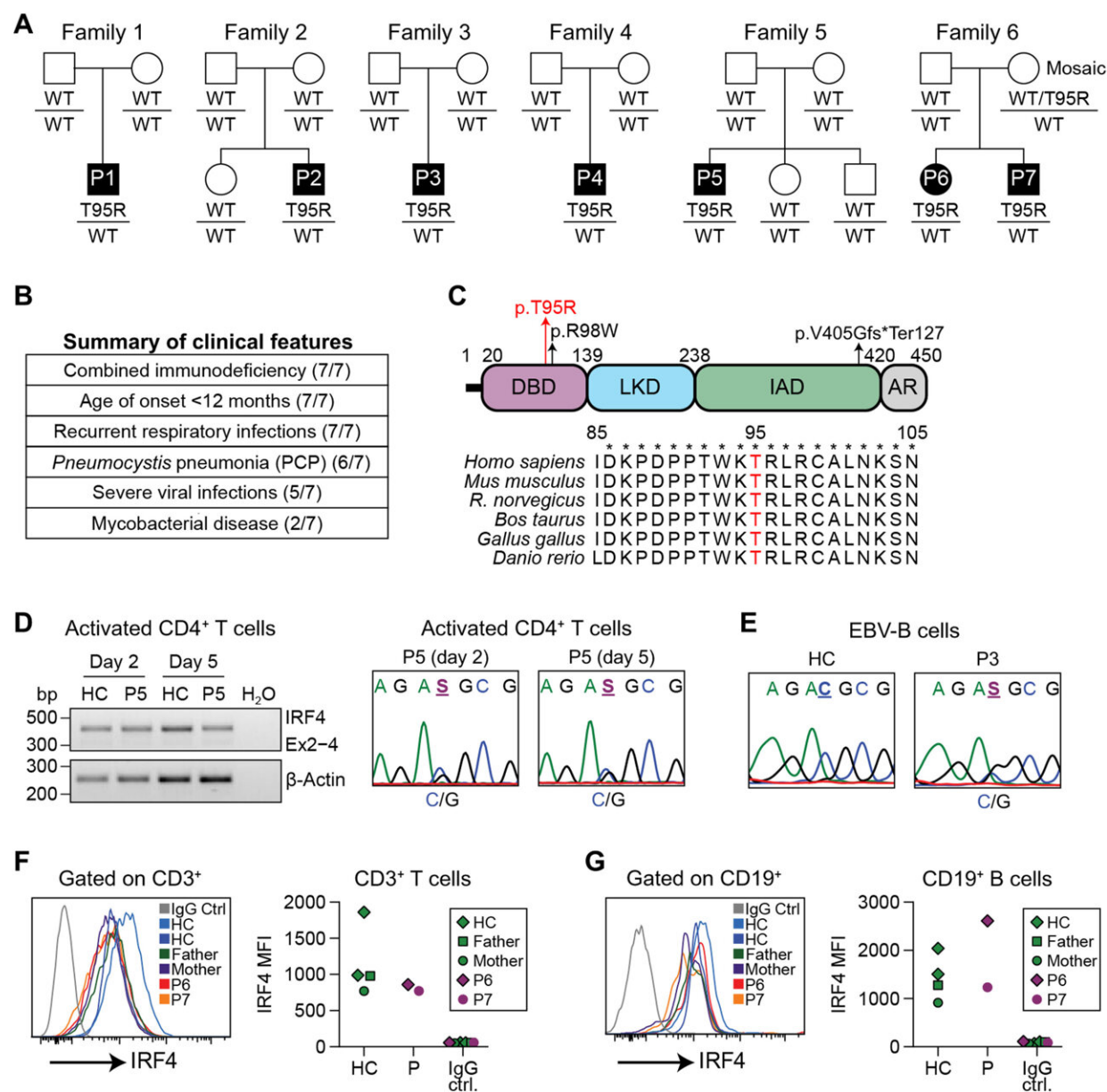


# Study reveals new genetic disorder that causes susceptibility to opportunistic infections

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Identification of a unique heterozygous mutation in the IRF4 gene in seven CID patients. Credit: *Science Immunology* (2023). DOI: 10.1126/sciimmunol.ade7953

An international consortium co-led by Vanderbilt University Medical Center immunogeneticist Rubén Martínez-Barricarte, Ph.D., has discovered a new genetic disorder that causes immunodeficiency and profound susceptibility to opportunistic infections including a life-threatening fungal pneumonia.

The discovery, reported Jan. 20 in the journal *Science Immunology*, will help identify people who carry this in-born error of immunity (IEI). "Our findings will provide the basis for [genetic diagnosis](#) and preventive treatment for these groups of patients," Martínez-Barricarte said.

IEIs, also known as primary immunodeficiencies, are [genetic defects](#) characterized by increased susceptibility to [infectious diseases](#), autoimmunity, anti-inflammatory disorders, allergy, and in some cases, cancer.

To date, 485 different IEIs have been identified. It is now thought that they occur in one of every 1,000 to 5,000 births, making them as prevalent as other genetic disorders, including cystic fibrosis and Duchene's muscular dystrophy.

Despite recent medical advances, about half of patients with IEIs still lack a genetic diagnosis that could help them avoid debilitating illness and death. That's why this research is so important.

The error in this case is a mutation in the gene for the protein IRF4, a

transcription factor that is pivotal for the development and function of B and T [white blood cells](#), as well as other immune cells.

As a postdoctoral fellow at The Rockefeller University, Martínez-Barricarte was part of an international research team that, in 2018, identified an IRF4 mutation associated with Whipple's disease, a rare bacterial infection of the intestine that causes diarrhea, weight loss, and abdominal and joint pain.

Martínez-Barricarte is now an assistant professor of Medicine in the Division of Genetic Medicine, and of Pathology, Microbiology & Immunology in the Division of Molecular Pathogenesis.

In 2020, after moving his lab to VUMC, he began collaborating with Aidé Tamara Staines-Boone, MD, and her colleagues in Monterrey, Mexico. They were caring for a young boy who was suffering from severe and recurrent fungal, viral, mycobacterial, and other infections.

Martínez-Barricarte and his team sequenced the protein-encoding regions of the boy's genome and discovered a de novo IRF4 mutation, which originated in the patient and was not inherited from his parents.

Upon consulting with IRF4 experts at the Imagine Institute for the study and treatment of genetic diseases in Paris, they were told that seven other groups were independently characterizing the same mutation. They now collaborate as the IRF4 International Consortium.

In the current study, the consortium identified seven patients from six unrelated families across four continents with profound combination immunodeficiency who experienced recurrent and serious infections, including pneumonia caused by the fungus *Pneumocystis jirovecii*. Each patient had the same mutation in the DNA-binding domain of IRF4.

Extensive phenotyping of patients' blood cells revealed immune cell abnormalities associated with the disease, including impaired maturation of antibody-producing B cells, and reduced T-cell production of infection-fighting cytokines.

Two knock-in mouse models, in which the mutation was inserted into the mouse genome, exhibited a severe defect in antibody production consistent with the combined immune deficiency observed in the patients.

The researchers also discovered the mutation had a "multimorphic" effect detrimental to the activation and differentiation of [immune cells](#).

While the mutant IRF4 binds to DNA with a higher affinity than the native form of the protein (in a hypermorphic way), its transcriptional activity in common, canonical genes is reduced (hypomorphic), and it binds to other DNA sites (in a neomorphic way), altering the protein's normal gene expression profile.

This multimorphic activity is a new mechanism for human disease. "We anticipate that variants with multimorphic activity may be more widespread in health and disease," the researchers concluded.

Co-authors from Martínez-Barricarte's lab included graduate students Jareb Pérez Caraballo and Xin Zhen, and research assistant Linh Tran.

**More information:** A multimorphic mutation in IRF4 causes human autosomal dominant combined immunodeficiency, *Science Immunology* (2023). [DOI: 10.1126/sciimmunol.ade7953](https://doi.org/10.1126/sciimmunol.ade7953)

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