

LETTER

Published October 5, 2026

DIAGNOSTIC CERTAINTY IN REGISTRY-BASED ESTIMATES OF INNATE AND INTRINSIC IMMUNITY DEFECTS

AUTHORSNezihe Köker Özer¹, Ercan Yılmaz², Erdem Topal²**AFFILIATED INSTITUTIONS**¹Inonu University, Faculty of Medicine, Department of Pediatrics, Malatya Türkiye²Inonu University, Faculty of Medicine, Pediatric Allergy and Immunology Department, Malatya, Türkiye**CORRESPONDING AUTHOR**

Nezihe Köker Özer

nezihe.koker@inonu.edu.tr**DOI**

10.20411/pai.v11i2.1108

SUGGESTED CITATION

Özer NK, Yılmaz E, Topal E. Diagnostic Certainty in Registry-Based Estimates of Innate and Intrinsic Immunity Defects. *Pathogens and Immunity*. 2026;11(2):127-129. doi: 10.20411/pai.v11i2.1108

This Letter refers to the article available at doi: [10.20411/pai.v10i2.845](https://doi.org/10.20411/pai.v10i2.845)

TO THE EDITOR,

We read with interest the study by Refaat et al describing defects of innate and intrinsic immunity in the Moroccan inborn errors of immunity (IEI) registry [1]. The cohort is particularly valuable because these disorders may remain unrecognized when routine immunological testing is unrevealing. We believe, however, that clarification of diagnostic certainty would strengthen interpretation of the reported frequency and genetic spectrum.

Of 884 patients with IEI, 79 (approximately 9%) were classified as having defects of innate or intrinsic immunity, whereas only 46 (58%) received a genetic diagnosis [1]. The Methods further state that both genetically confirmed patients and those with clinical or biological findings “suggestive of the condition” were included. The operational criteria used to classify the remaining

33 genetically unresolved patients are not provided. This distinction is important because immunoglobulin concentrations and lymphocyte subsets were largely normal in the cohort, and disorders in this category may require pathway-specific functional testing and/or molecular evidence. Without separating confirmed, probable, and possible diagnoses, the reported 9% may represent a mixture of diagnostic certainty levels rather than the frequency of confirmed innate or intrinsic IEL.

Diagnostic certainty also matters within the genetically resolved group. Table 5 lists variants in *STAT1*, *IFNGR1*, *IFIH1*, *POLR3A*, *SNORA31*, and other genes, but variant-level ACMG/AMP classification, segregation results, and patient-specific functional evidence are not reported [1]. American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) recommendations incorporate population, computational, functional, and segregation evidence when assigning variant pathogenicity [2].

STAT1 provides a clinically relevant example. In the cohort, *STAT1* variants are assigned to both Mendelian susceptibility to mycobacterial disease and chronic mucocutaneous candidiasis [1]. Yet loss-of-function and gain-of-function *STAT1* variants produce different biological and clinical phenotypes [3, 4]. This distinction can affect surveillance and treatment, including consideration of JAK inhibition in selected patients with *STAT1* gain-of-function disease [4]. Thus, functional direction is not merely descriptive; it can influence clinical management. The 2024 International Union of Immunological Societies (IUIS) classification likewise distinguishes disorders caused by different functional effects of variants within the same gene [5].

We therefore suggest reporting the diagnostic criteria and functional evidence used for the 33 genetically unresolved patients and, for genetically resolved cases, the pathogenicity classification, segregation status, and functional validation of each variant. Stratifying the cohort by diagnostic certainty would preserve the value of this registry while making the 9% estimate more reproducible and clinically interpretable.

ACKNOWLEDGMENTS

The authors acknowledge the use of OpenAI ChatGPT (5.6 Sol) for language editing. AI-assisted text was reviewed, revised, and approved by all authors.

FUNDING

No funding was received for this work.

POTENTIAL CONFLICTS OF INTERESTS

The authors declare no relevant conflicts of interest.

REFERENCES

1. Refaat M, Oujane C, Errami A, Aadam Z, Moundir A, Baghdad B, Zaidi S, Kholaiq H, El Kettani A, Benhsaien I, Ailal F, Bourhanbour AD, El Bakkouri J, Bousfiha AA. Defects in Innate and Intrinsic Immunity in Morocco: A Retrospective Analysis of the Genetic Landscape and Clinical Correlations. *Pathog Immun.* 2025;10(2):243–55. doi: [10.20411/pai.v10i2.845](https://doi.org/10.20411/pai.v10i2.845). PubMed PMID: 41209815; PMCID: PMC12594312.

2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–24. [doi: 10.1038/gim.2015.30](https://doi.org/10.1038/gim.2015.30). PubMed PMID: 25741868; PMCID: PMC4544753.
3. Zhang W, Chen X, Gao G, Xing S, Zhou L, Tang X, Zhao X, An Y. Clinical Relevance of Gain- and Loss-of-Function Germline Mutations in Stat1: A Systematic Review. *Front Immunol*. 2021;12:654406. [doi: 10.3389/fimmu.2021.654406](https://doi.org/10.3389/fimmu.2021.654406). PubMed PMID: 33777053; PMCID: PMC7991083.
4. Asano T, Noma K, Mizoguchi Y, Karakawa S, Okada S. Human Stat1 Gain of Function with Chronic Mucocutaneous Candidiasis: A Comprehensive Review for Strengthening the Connection between Bedside Observations and Laboratory Research. *Immunol Rev*. 2024;322(1):81–97. [doi: 10.1111/imr.13300](https://doi.org/10.1111/imr.13300). PubMed PMID: 38084635.
5. Poli MC, Aksentijevich I, Bousfiha AA, Cunningham-Rundles C, Hambleton S, Klein C, Morio T, Picard C, Puel A, Rezaei N, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I, Tangye SG. Human Inborn Errors of Immunity: 2024 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Hum Immun*. 2025;1(1):e20250003. [doi: 10.70962/jhi.20250003](https://doi.org/10.70962/jhi.20250003). PubMed PMID: 41608114; PMCID: PMC12829761.

Footnotes

Submitted August 26, 2026 | Accepted September 14, 2026 | Published October 5, 2026

Copyright

Copyright © 2026 The Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License.