Letter

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# Response to: "Diagnostic Certainty in Registry-Based Estimates of Innate and Intrinsic Immunity Defects"

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We thank Dr. Köker Özer and colleagues for carefully reading our article, "Defects in Innate and Intrinsic Immunity in Morocco: A Retrospective Analysis of the Genetic Landscape and Clinical Correlations," and for their constructive comments. We welcome this opportunity to clarify the diagnostic framework used in our retrospective study, the interpretation of the genetic findings, and the distinction between STAT1-associated phenotypes.

## COMMENT 1

The authors express concern that the 79 patients classified as having innate or intrinsic immunity defects included both genetically confirmed cases and patients whose diagnoses were based on suggestive clinical or biological findings. They note that the operational criteria for the 33 patients without a genetic diagnosis were not sufficiently detailed.

### Response

We thank the authors for raising this important point. We agree that distinguishing genetically confirmed diagnoses from cases supported by clinical and biological evidence is essential when interpreting retrospective registry data.

As described in our manuscript, innate and intrinsic immunity defects can be challenging to diagnose because patients may present with characteristic, recurrent, severe, or unusual infections despite largely normal routine immunological findings. The clinical and immunological characteristics of our cohort are presented in Tables 2–4.

Furthermore, as discussed in our article, access to molecular diagnostic investigations in our setting is constrained by the availability of specialized facilities and the high cost of genetic testing. This context is relevant because genetic confirmation was obtained in 46 of the 79 patients classified within the innate and intrinsic immunity group.

The remaining patients were included on the basis of clinical and/or biological findings suggestive of these disorders, as stated in the Methods section. We acknowledge that the published results do not separately detail the diagnostic evidence and certainty level for each of these patients.

The proportion of approximately 9% therefore reflects the representation of this group within our retrospective Moroccan inborn errors of immunity (IEI) registry, rather than a population-based estimate of genetically confirmed disease. We appreciate the authors' emphasis on the importance of clearly distinguishing genetic confirmation from clinical classification when interpreting registry-based findings.

## COMMENT 2

The authors note that Table 5 does not provide variant-level American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG)/(AMP) classifications, segregation results, or patient-specific functional evidence for all reported genetic findings.

### Response

We thank the authors for highlighting the importance of detailed variant interpretation, including ACMG/AMP classification, segregation analysis, and functional validation.

In our study, whole-exome sequencing was the principal genetic diagnostic approach, complemented by bioinformatic analyses and functional investigations, including IL-12 and IFN-γ assays, when available. We acknowledge that the published table summarizes the identified genes, modes of inheritance, and variants but does not provide a comprehensive presentation of the supporting evidence for each variant.

We are currently preparing a separate manuscript focused on the bioinformatic analysis and classification of the variants identified in our cohort. This work aims to provide a more detailed assessment of the genetic findings and their potential clinical relevance. We recognize that bioinformatic predictions constitute one component of variant interpretation and should be considered alongside available clinical, segregation, and functional evidence.

In addition, our laboratory has contributed to the characterization of several innate and intrinsic immunity disorders through disease-specific publications. These include studies addressing the clinical, immunological, and genetic features of Mendelian susceptibility to mycobacterial disease (MSMD), including Moroccan patients [1, 2] as well as genetic predisposition to mucocutaneous fungal infections [3] . These publications provide complementary context for understanding the clinical phenotypes and underlying immune defects observed in our cohort.

We appreciate the authors' constructive comments, which highlight the importance of comprehensive genetic characterization in studies of innate and intrinsic immunity defects.

### COMMENT 3

The authors emphasize that *STAT1* variants associated with Mendelian susceptibility to mycobacterial disease (MSMD) and chronic mucocutaneous candidiasis (CMC) can have different functional consequences and clinical implications.

### Response

We appreciate this important observation and would like to clarify that our manuscript distinguishes between the *STAT1*-associated phenotypes observed in our cohort.

Among patients with MSMD, *STAT1* variants were described in the context of autosomal-dominant partial *STAT1* deficiency. In contrast, the *STAT1* variants associated with CMC were classified in the context of *STAT1* gain-of-function (GOF). These conditions were not considered functionally equivalent.

As discussed in our manuscript, impaired *STAT1*-dependent IFN-γ signaling can compromise antimycobacterial immunity, whereas *STAT1* GOF is associated with sustained *STAT1* phosphorylation and impaired Th17-cell differentiation, contributing to susceptibility to chronic mucocutaneous candidiasis.

Thus, the distinction between these phenotypes and their underlying mechanisms was addressed in the original article. We nevertheless agree with the authors that more detailed variant-level functional evidence would help readers assess the molecular interpretation of individual cases and further clarify the relationship between genotype, immune dysfunction, and clinical presentation.

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## POTENTIAL CONFLICTS OF INTEREST

The authors report no relevant conflicts of interest.

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## Footnotes

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