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The many faces of RAG deficiency

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The diagnosis of severe combined immunodeficiency (SCID), the most severe type of inborn error of immunity (IEI), has traditionally relied on a familiar triad: severe or opportunistic infections, profound T-cell lymphopenia, and early infancy. Yet, as our understanding of IEI has expanded, so has the recognition that SCID is not always clinically straightforward. In this issue of *Haematologica,* Brillant-Marquis and colleagues describe an infant with a compound heterozygous mutation in recombination activating gene (*RAG) 1* who initially presented not with an overwhelming infection or lymphopenia, but with immune thrombocytopenia, erythroderma, and a normal absolute lymphocyte count (ALC). Their report serves as a timely reminder that immune dysregulation may be the first manifestation of RAG1/2 deficiency, and that a normal ALC and lack of previous infections do not necessarily imply normal adaptive immunity.[1]

Few monogenic disorders illustrate phenotypic diversity as strikingly as RAG1/2 deficiency. RAG1 and RAG2 initiate V(D)J recombination by introducing DNA double-strand breaks at recombination signal sequences (RSSs), enabling assembly of diverse antigen receptors.[2] Their central role in adaptive immunity became evident through the seminal work of Mombaerts and colleagues, who generated *Rag1*-knockout mice lacking mature T and B lymphocytes due to failure of V(D)J recombination.[3] This experimental model provided the biological framework for understanding the first patients with biallelic *RAG1*/2 mutations reported four years later by Schwartz et al.[4] Since then, RAG deficiency has evolved from a prototype of classical T-B-NK+ SCID into a much broader clinical spectrum encompassing Omenn syndrome, leaky SCID, combined immunodeficiency with granulomatous disease and autoimmunity, idiopathic CD4 lymphopenia, common variable immunodeficiency-like phenotypes, and autoimmune features due to immune dysregulation.[5] Accordingly, the level of residual recombinase activity, rather

than genotype itself, has emerged as a major determinant of clinical phenotype. Rather than representing distinct diseases, these conditions are increasingly viewed as a continuum resulting from varying degrees of residual V(D)J recombination activity and/or additional genetic and immunological modifiers.[6]

This expanding clinical spectrum reflects the central role of RAG1 and RAG2 in adaptive immunity. By initiating V(D)J recombination, RAG proteins enable the generation of diverse T- and B-cell receptors. Complete loss of recombinase activity abolishes T and B lymphocyte development, whereas hypomorphic variants enable limited receptor rearrangement, resulting in the emergence of restricted, oligoclonal lymphocyte populations. Although these residual lymphocytes provide partial immune function, they may escape central and peripheral tolerance, thereby promoting autoimmunity, inflammation, and tissue infiltration. Impaired thymic expression of autoimmune regulator (AIRE), defective negative selection, and reduced regulatory T-cell subsets have all been implicated in the breakdown of immune tolerance. Consequently, immune dysregulation and autoimmunity may represent the initial manifestations of RAG deficiency, preceding recurrent or severe infections.[6]

The case presented by Brillant-Marquis and colleagues exemplifies this diagnostic challenge. Severe thrombocytopenia represented the initial manifestation, preceding recognition of profound T-cell dysfunction. Importantly, the patient's ALC remained within the normal range and lacked severe infections, findings that could easily delay consideration of SCID. Only detailed immunophenotyping revealed the complete absence of naive T cells, profound B-cell lymphopenia, impaired lymphocyte proliferation, and the presence of maternal T-cell engraftment. Together, these findings established the diagnosis of SCID.

The presence of circulating maternal T cells further highlights another important diagnostic pitfall. Infants with SCID may harbor maternally derived allogeneic T lymphocytes that survive because of defective host immunity. These cells can cause graft-versus-host disease-like manifestations, including erythroderma, hepatitis, and enteropathy, closely resembling Omenn syndrome. Distinguishing maternal T-cell engraftment from autologous oligoclonal T-cell expansion is clinically important because both conditions arise from different immunopathogenic mechanisms, although each ultimately requires early hematopoietic stem cell transplantation (HSCT). Chimerism analysis using fluorescence in situ hybridization (FISH) or short tandem repeat (STR) analysis is essential for confirming maternal T-cell engraftment.

More broadly, this report illustrates how the diagnostic approach to SCID has fundamentally changed over the past two decades. Historically, diagnosis relied largely on clinical recognition after recurrent severe, life-threatening infections which had already caused organ damage. The implementation of newborn screening (NBS) using T-cell receptor excision circles (TRECs) has transformed this paradigm by identifying infants before clinical deterioration.[7] NBS has also demonstrated that RAG1/2 deficiency is among the most common genetic causes of SCID in the United States, accounting for approximately 11-15% of all SCID cases identified through NBS and over 40% of leaky SCID and Omenn syndrome.[6,8] However, NBS does not eliminate the need for clinical vigilance. As this case demonstrates, patients born before screening implementation or in regions where universal screening is unavailable may still present with atypical manifestations that may evade an early diagnosis.

Equally important is the recognition that lymphocyte enumeration alone is no longer sufficient. Comprehensive immune evaluation should include assessment of naive T-cell populations,

lymphocyte function, T-cell receptor repertoire, and increasingly, rapid molecular diagnosis through next-generation sequencing. Modern genomic technologies continue to reveal the remarkable phenotypic heterogeneity associated with *RAG* mutations while facilitating earlier diagnosis and genetic counseling.

Therapeutic advances have paralleled these diagnostic developments. Early HSCT performed before the onset of severe infections has dramatically improved survival, making timely recognition of atypical presentations critically important.[9] Refinements in donor selection, conditioning regimens, and graft manipulation have further enhanced outcomes for patients lacking matched donors. Gene therapy and genome editing hold particular promise for RAG deficiency. Lentiviral gene addition has demonstrated encouraging preclinical results, while CRISPR-based targeted correction of hematopoietic stem cells offers the prospect of restoring physiological RAG expression while preserving endogenous regulatory control.[10] These approaches illustrate how a deeper understanding of RAG biology is being translated into therapies that target the root cause of disease.

The report by Brillant-Marquis and colleagues reminds us that the phenotype of RAG deficiency extends well beyond the classical image of an infant with profound lymphopenia and overwhelming infection. For hematologists, dermatologists, pediatricians, and immunologists alike, early-onset autoimmune cytopenias, inflammatory skin disease, or unexplained immune dysregulation should prompt careful evaluation of adaptive immune function, even when lymphocyte counts appear normal. Ultimately, the promise of precision medicine for RAG deficiency depends not only on better therapies, but also on recognizing its many faces before irreversible complications develop.

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Legend to figure:

Figure 1. Evolution of RAG deficiency: from gene discovery to precision medicine.

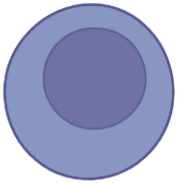
1992:
Basic biology

- *Rag1 -/-* mice
- Loss of V(D)J recombination
- Absent mature T and B cells

1996:
Human genetics

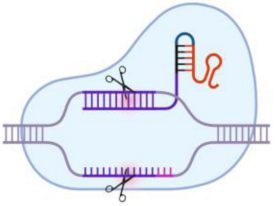
- First patients with *RAG1,2* deficiency
- Classical T-B-NK+ SCID

2000s:
Expanding clinical spectrum



- Omenn syndrome
- Leaky SCID
- Maternal T-cell engraftment
- CID
- CVID-like
- Autoimmunity
- Granulomas

Present and future:
Precision medicine



Diagnosis:
- TREC NBS
- WES / WGS

Therapy:
- Early HSCT
- Gene addition
- Genome editing

Increasing understanding of *RAG* biology, clinical heterogeneity, and precision medicine