**Editorial Perspective**

Turk J Immunol 2024;12(Suppl 1):1-5
DOI: 10.4274/tji.galenos.2024.00001

# Tracing the Spectrum of Inborn Errors of Immunity from Past to Present

**Safa Barış[1,2,3,*], Talal A. Chatila[4,5,*]**

[1]Division of Pediatric Allergy and Immunology, Marmara University Faculty of Medicine, İstanbul, Turkey
[2]İstanbul Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Marmara University, İstanbul, Turkey
[3]The Işıl Berat Barlan Center for Translational Medicine, Marmara University, İstanbul, Turkey
[4]Division of Immunology, Boston Children's Hospital, Boston, Massachusetts, USA
[5]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA
*Corresponding authors

**Cite as:** Barış S, Chatila TA. Tracing the Spectrum of Inborn Errors of Immunity from Past to Present. Turk J Immunol 2024;12(Suppl 1):1-5

**Received:** 23.10.2023 **Accepted:** 30.10.2023

**Corresponding Author:** Talal A. Chatila, Division of Immunology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, MA, USA; Safa Barış, Division of Pediatric Allergy and Immunology, Marmara University Faculty of Medicine, İstanbul Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, The Işıl Berat Barlan Center for Translational Medicine, İstanbul, Turkey
**E-mail:** talal.chatila@childrens.harvard.edu; safabaris@hotmail.com **ORCID:** orcid.org/0000-0001-7439-2762; 0000-0002-4730-9422

**Abstract**

Human inborn errors of immunity (IEI) constitute a constellation of genetic disorders with profound implications for immune system function, leading to recurrent infections, immune dysregulations, and malignancies. The field of IEI has undergone a tremendous evolution over the course of seventy years, with substantial strides in comprehending the clinical and immunological aspects of monogenic disorders. Furthermore, these endeavors have synergized with innovative therapeutic modalities, forging a trajectory toward enhanced patient care. These advances promise to favorably transform the outcomes of many IEI to provide patients with increased life expectancy and improved quality of life. In this special issue of the Turkish Journal of Immunology, we will survey some recent advances in the field of IEI with a focus on disease pathogenesis and outcomes.

**Keywords:** Inborn errors of immunity, primary immune deficiencies, diagnosis, treatment, outcome

## Overview of Inborn Errors of Immunity

Human inborn errors of immunity (IEI), previously termed primary immunodeficiency disorders, have a historical lineage dating back seven decades. The narrative of these diseases started with the seminal identification of agammaglobulinemia as the causative disorder in a boy with recurrent bacterial infections in 1952 (1). This description was followed in 1958 by a report of several Swiss infants with alymphocytosis and agammaglobulinemia, receiving the designation of Swiss-type agammaglobulinemia (2). Studies of patients with IEI diseases have taught us much about the complexities of the way that our immune system develops and functions. Following Miller's (3) discovery in 1961 of the immunological roles of the thymus, Cooper (4) discovered the dual roles of the thymus and bursa-dependent cell lineages, achieving the concept of T and B lymphocytes and adaptive immunity in 1965 (4). This concept enabled us to classify Bruton and Swiss agammaglobulinemia as B- and T-cell deficiencies, revealing the essential role of these cells in protection against infections. Specific therapies for IEI came swiftly in the intervening years after their discovery. Starting with the use of gammaglobulins for antibody deficiency by Ogden Bruton, Charles Janeway, and David Gitlin (5,6), this was continued with the first pioneer-matched allogeneic hematopoietic stem cell transplantation (HSCT) by Robert Good and his colleagues in 1968 (7). At around that time, Humphrey Kay and his colleagues developed thymic transplantation for DiGeorge syndrome (8). These steps symbolized heroic interventions for diseases previously deemed incurable and most often fatal.

Despite the strides in the clinical management of IEI, elucidating disease-associated genes has been a protracted endeavor spanning several decades. For instance, Ataxia-telangiectasia was first reported in 1926 by two Czech neurologists (9), while the discovery of the responsible

*ATM* gene was in 1995. In that regard, studies on Ataxia-telangiectasia by Ahmet İzzet Berkel were foundational in initiating the field of IEI in Turkey (10). A similar time trajectory is also noted for X-linked agammaglobulinemia, which took over 40 years to unravel its genetic underpinnings (11), as well as Swiss-type agammaglobulinemia whose genetic causation was established in 1993, 35 years following the initial description of the disease (12). The prototype disorder of primary immune dysregulation is immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), leading to impaired $CD4^+CD25^+$ regulatory T-cells (Tregs) production was first defined in 1982, while mutations in the causative gene Forkhead Box P3 (*FOXP3*) were discovered in 2000 by different groups (13,14). All these and many other discoveries elicit the critical role of clinical observations that drive bedside to bench investigation to reveal the responsible gene defects for the respective disorders. It was no coincidence that advances in the field of IEI took place within the context of the impressive progress in molecular genetics in the second half of the 20$^{th}$ century and were especially propelled by gene sequencing methods epitomized by those established by Sanger in 1977, leading to the discovery of numerous genetic mutations (15).

More recently, the past 15 years have witnessed rapid advances in high-throughput next-generation sequencing technologies that proved highly productive in the field of IEI. These enabled a vast body of translational research, spurred by the identification of many new genetic causes of IEI (16). The most recent classification of IEI by the International Union of Immunological Sciences provides numerous single gene defects responsible for unique IEI, including 485 genes (17). This classification extends the concept of IEI to include not only defects affecting the adaptive immune system but also more diverse and complex ones, including those impacting innate immunity, diseases associated with somatic mutations and autoantibodies, and genetic defects extrinsic to the hematopoietic system. Furthermore, studies on monogenic disorders led to the identification of distinct clinical phenotypes caused by different mutations affecting the same gene, resulting in amorphic or hypomorphic loss-of-function or, on the opposite side, gain-of-function properties in the target proteins (18,19). Further complexity emerged in defining the mode of genetic dominance in IEI, with new insights into dominant-negative, haploinsufficient, and neomorphic inheritance (20,21). Consequently, IEI is now appreciated to give rise to diverse clinical diseases and phenotypes ranging from classically infectious ones such as recurrent infections caused by a broad range of microorganisms to very narrow susceptibility to particular infections and also non-infectious phenotypes presenting with autoimmunity, autoinflammation, and malignancy (22-24).

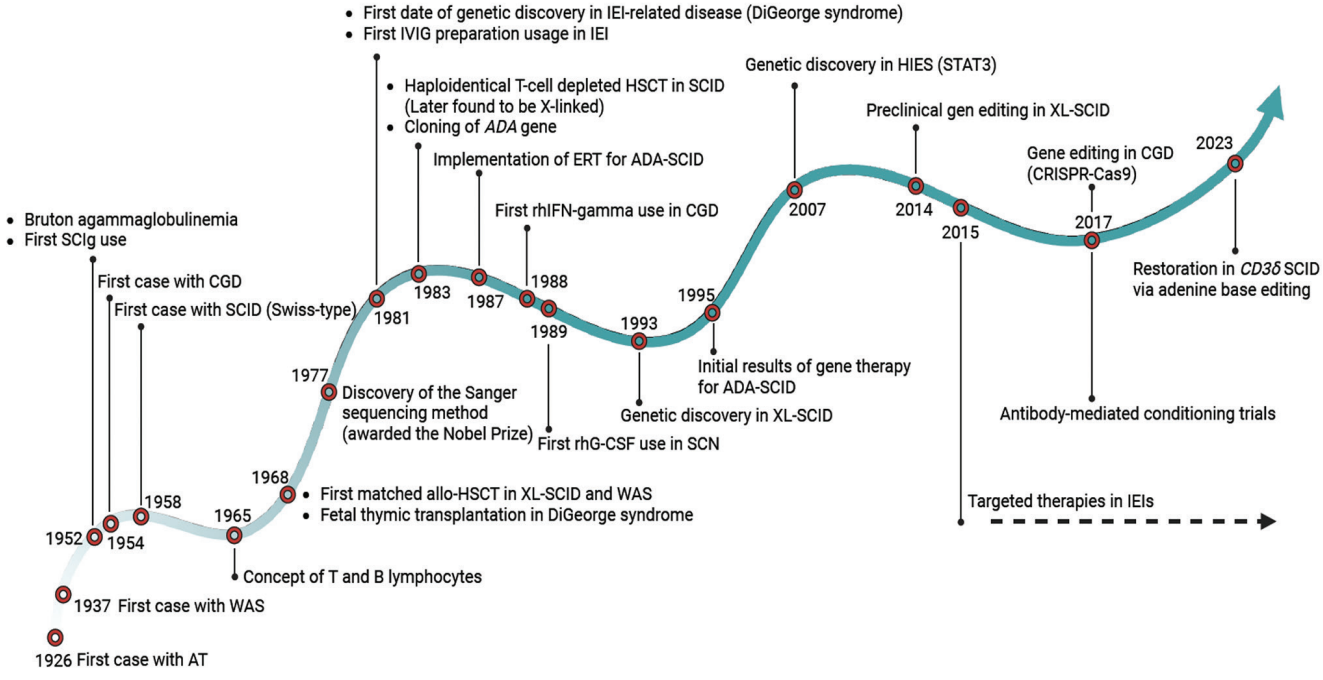


**Figure 1.** The major development steps in IEI over time.
ADA: Adenosine deaminase, AT: Ataxia telangiectasia, CGD: Chronic granulomatous disease, ERT: Enzyme replacement therapy, HSCT: Hematopoietic stem cell transplantation, IVIG: Intravenous immunoglobulin, SCID: Severe combined immunodeficiency, SCN: Severe congenital neutropenia, SCIG: Subcutaneous immunoglobulin, rhIFN: Recombinant human interferon, rhG-CSF: Recombinant human granulocyte-colony stimulant factor, XL: X-linked, WAS: Wiskott-Aldrich syndrome. Created by BioRender.

**Table 1.** Current available targeted therapies for IEI

| Targeted protein | Molecule | Diseases |
|---|---|---|
| mTOR inhibitor | Sirolimus, everolimus | IPEX, CD25 and CD122 deficiencies, ALPS, LRBA deficiency, CTLA4 insufficiency, NLRC4-GOF |
| B7-1 (CD80) binding<br>B7-2 (CD86) binding | Abatacept | LRBA deficiency, CTLA4 insufficiency (NCT03733067, DRKS00017736), DEF6 deficiency |
| B7-1 (CD80) binding<br>B7-2 (CD86) binding | Belatacept | CTLA4 insufficiency |
| JAK1 and JAK2 inhibitor | Ruxolitinib | STAT1/3-GOF, HLH, STAT6-GOF, AGS, SAVI, STAT2 R148-LOF, HCK-GOF, STAT5B-GOF, COPA deficiency, SOCS1 haploinsufficiency |
| | Baricitinib | STAT1-GOF, CANDLE, AGS, SAVI, COPA deficiency, SOCS1 haploinsufficiency |
| JAK1 and JAK3 inhibitor | Tofacitinib | STAT3-GOF, STAT6-GOF, CANDLE, AGS, SAVI, PSMB9-GOF, SOCS1 haploinsufficiency |
| P110delta inhibitor | Leniolisib | APDS (NCT02435173, NCT05438407, NCT02859727) |
| IL4R-α inhibitor | Duplimuab | STAT6-GOF |
| TNF-α inhibitor | Etanercept | DADA2, CANDLE, NEMO deficiency, IKBKG (NEMO exon 5 deletion), TBK1 deficiency |
| | Infliximab | |
| | Adalimumab | |
| CD20 inhibitor | Rituximab | ALPS, APDS, ALPS-like, APECED, IPEX |
| IL-12/IL-23 inhibitor | Ustekinumab | CGD/LAD-1 |
| IL-1R inhibitor | Anakinra | CAPS (MWS, NOMID, FACS), FMF, TRAPS, HIDS, DIRA, CGD, CDC42 deficiency, C2orf69 deficiency |
| IL-1β inhibitor | Canakinumab | CAPS (MWS, NOMID, FACS), DIRA, CDC42 deficiency |
| | Rilonacept | |
| CD52 inhibitor | Alemtuzumab | HLH |
| IFN-γ inhibitor | Emapalumab | HLH |
| IL-6R inhibitor | Tocilizumab | STAT3-GOF, RIPK1 deficiency |
| C5 inhibitor | Eculizumab, Pozelimab | CD55 deficiency (NCT04209634) |
| IL-18 binding protein | Tadekinig-α | NLRC4-GOF, XIAP (NCT03512314) |
| CXCR4 antagonist | Plerixafor | WHIM (NCT01058993) |
| α4β7 integrin antagonist | Vedolizumab | XLA |

AGS: Aicardi-Goutieres syndrome, ALPS: Autoimmune lymphoproliferative syndrome, APDS: Activated phosphoinositide 3-kinase delta syndrome, APECED: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, CANDLE: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, CAPS: Cryopyrin-associated periodic syndrome, CDC42: Cell division cycle 42, CGD: Chronic granulomatous disease, CID: Combined immunodeficiency, COPA: Coatomer protein subunit α, C2orf69: Chromosome 2 open reading frame 69, CTLA-4: Cytotoxic T lymphocyte antigen-4, DADA2: Deficiency of adenosine deaminase, DEF6: DEF6 guanine nucleotide exchange factor, DIRA: Deficiency of IL-1 Receptor Antagonist (IL-1RA), FACS: familial cold autoinflammatory syndrome, HCK-GOF: Hematopoietic cell kinase-gain-of-function, FMF: familial Mediterranean fever, HIDS: Hyper IgD syndrome, HLH: Hemophagocytic lymphohistiocytosis, IL-1R: Interleukin-1 receptor, IL-1β: Interleukin-1 beta, IL-6R: Interleukin-6 receptor, IKBKG (NEMO exon 5 deletion): Inhibitor of kappa polypeptide gene enhancer in B-cells, Kinase Gamma/Nuclear Factor κB, Essential Modulator, IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked, JAK: Janus Kinase, LAD-1: Leukocyte adhesion defect type 1, LOF: Loss-of-function, LRBA: Lipopolysaccharide-responsive and beige-like anchor protein, mTOR: Mammalian target of rapamycin, NEMO: Nuclear factor-kappa B essential modulator, NLRC4-GOF: NLR family CARD domain containing 4 gain-of-function, NOMID: Neonatal-onset multisystem inflammatory disease, PSMB9-GOF: Proteasome subunit beta type-9-gain-of-function, RIPK1: Receptor interacting serine/threonine protein kinase 1, SAVI: STING-associated vasculopathy with onset in infancy, SOCS1: Suppressors of cytokine signaling, STAT3-GOF: Signal transducer and activator of transcription 3 gain-of-function, STAT1-GOF: Signal transducer and activator of transcription 1 gain-of-function, STAT6-GOF: Signal transducer and activator of transcription 6 gain-of-function, TBK1: TANK binding kinase 1, TNF-α: Tumor necrosis factor alpha, TRAPS: Tumor necrosis factor receptor-associated periodic syndrome, XLA: X-lined agammaglobulinemia, XIAP: X-linked inhibitor of apoptosis protein, WHIM: Warts, hypogammaglobulinemia, infections, and myelokathexis.

The advancements in our understanding of IEI stimulated in turn striking innovations in therapies. While the focus of first-generation therapies, such as immunoglobulin replacement therapy and antimicrobial prophylaxis, was on protection from disease complications, subsequent therapies evolved to offer precision therapies and curative interventions. An example of the former includes Janus kinase inhibitors for JAK and STAT protein gain of function disorders and CTLA4-Ig therapy for a variety of immune dysregulatory diseases (25-28). An example of the latter is HSCT, whose widespread application was propelled by advances in haploidentical transplantation and preclinical attempts for the single agent conditioning with CD45-antibody drug conjugate or humanized anti-CD117 antibody. Other examples include thymus transplantation and new-generation gene therapies. Promising future developments include organoid-based treatment (Using patient-derived induced pluripotent stem cells (iPSCs) and

an *in vitro* artificial thymic organoid system) and genome-editing approaches (gene and base editing) (16,29-33). Furthermore, global patient registries and collaborative research efforts have facilitated data sharing and expertise, accelerating the understanding and management of IEI. These seminal achievements in the IEI era are presented in Figure 1. Moreover, increasing awareness of immunological pathways linked to the respective disorders promotes the use of precision therapies aimed at specific molecular targets, which usually offer better disease control than known classical treatments (Table 1).

With the above background in mind, in this issue, we will highlight the different aspects of IEI by focusing on special relevant areas. These include a historical overview of the field of IEI as seen from the perspective of its development in Turkey, a country with a long tradition of studying these disorders. Specific disease manifestations are surveyed in reviews on pulmonary complications in monogenic CVID disorders and the outcome of SARS-CoV-2 infection in IEI patients. Other reviews will address novel molecular mechanisms operative in immune dysregulatory diseases, including STAT1, STAT3, and STAT6 GOF diseases, LRBA deficiency, monogenic inflammatory bowel diseases, and primary atopic disorders. We also survey advances in immunoglobulin replacement therapy based on new therapeutic formulations and their application in IEI. Overall, we hope that these reviews would prove helpful in showcasing the guiding concepts in the area of IEI and also highlighting the exciting recent advances in this field.

## References


1. Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9:722-8.
2. Hitzig WH, Biro Z, Bosch H, Huser HJ. [Agammaglobulinemia & alymphocytosis with atrophy of lymphatic tissue]. Helv Paediatr Acta. 1958;13:551-85.
3. Miller JF. Immunological function of the thymus. Lancet. 1961;2:748-9.
4. Cooper MD, Peterson RD, Good RA. Delineation of the thymic and bursal lymphoid systems in the chicken. Nature. 1965;205:143-6.
5. Bruton OC, Apt L, Gitlin D, Janeway CA. Absence of serum gamma globulins. AMA Am J Dis Child. 1952;84:632-6.
6. Gross PA, Gitlin D, Janeway CA. The gamma globulins and their clinical significance. IV. Therapeutic uses of gamma globulins. N Engl J Med. 1959;260:170-8 concl.
7. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet. 1968;2:1366-9.
8. Cleveland WW, Fogel BJ, Brown WT, Kay HE. Foetal thymic transplant in a case of Digeorge's syndrome. Lancet. 1968;2:1211-4.
9. Syllaba L HK. Contribution a l'independance de l'athetose double idiopathique et congenitale. Rev Neurol. 1926;1:541-62.
10. Berkel AI, Ersoy F, Epstein LB, Spitler LE. Transfer factor therapy in ataxia--telangiectasia. Clin Exp Immunol. 1977;29:376-84.
11. Vetrie D, Vorechovsky I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature. 1993;361:226-33.
12. Noguchi M, Yi H, Rosenblatt HM, Filipovich AH, Adelstein S, Modi WS, et al. Interleukin-2 receptor gamma chain mutation results in X-linked severe combined immunodeficiency in humans. Cell. 1993;73:147-57.
13. Chatila TA, Blaeser F, Ho N, Lederman HM, Voulgaropoulos C, Helms C, et al. JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic disregulation syndrome. J Clin Invest. 2000;106:R75-81.
14. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet. 2001;27:20-1.
15. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A. 1977;74:5463-7.
16. Baris S, Abolhassani H, Massaad MJ, Al-Nesf M, Chavoshzadeh Z, Keles S, et al. The Middle East and North Africa Diagnosis and Management Guidelines for inborn errors of immunity. J Allergy Clin Immunol Pract. 2023;11:158-80 e11.
17. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42:1473-507.
18. Notarangelo LD, Bacchetta R, Casanova JL, Su HC. Human inborn errors of immunity: An expanding universe. Sci Immunol. 2020;5.
19. Kolukisa B, Baris S. Primary immune regulatory disorders and targeted therapies. Turk J Haematol. 2021;38:1-14.
20. Boisson B, Quartier P, Casanova JL. Immunological loss-of-function due to genetic gain-of-function in humans: autosomal dominance of the third kind. Curr Opin Immunol. 2015;32:90-105.
21. Thouenon R, Chentout L, Moreno-Corona N, Poggi L, Lombardi EP, Hoareau B, et al. A neomorphic mutation in the interferon activation domain of IRF4 causes a dominant primary immunodeficiency. J Exp Med. 2023;220.
22. Li J, Vinh DC, Casanova JL, Puel A. Inborn errors of immunity underlying fungal diseases in otherwise healthy individuals. Curr Opin Microbiol. 2017;40:46-57.
23. Delafontaine S, Meyts I. Infection and autoinflammation in inborn errors of immunity: brothers in arms. Curr Opin Immunol. 2021;72:331-9.
24. Baris S, Kolukisa B. Immune dysfunction in inborn errors of immunity causing malignancies. Expert Rev Clin Immunol. 2021;17:695-9.
25. Baris S, Alroqi F, Kiykim A, Karakoc-Aydiner E, Ogulur I, Ozen A, et al. Severe early-onset combined immunodeficiency due to heterozygous gain-of-function mutations in STAT1. J Clin Immunol. 2016;36:641-8.
26. Baris S, Benamar M, Chen Q, Catak MC, Martinez-Blanco M, Wang M, et al. Severe allergic dysregulation due to a gain of function mutation in the transcription factor STAT6. J Allergy Clin Immunol. 2023;152:182-94 e7.

27. Kiykim A, Ogulur I, Dursun E, Charbonnier LM, Nain E, Cekic S, et al. Abatacept as a long-term targeted therapy for LRBA deficiency. J Allergy Clin Immunol Pract. 2019;7:2790-800 e15.

28. Taghizade N, Babayeva R, Kara A, Karakus IS, Catak MC, Bulutoglu A, et al. Therapeutic modalities and clinical outcomes in a large cohort with LRBA deficiency and CTLA4 insufficiency. J Allergy Clin Immunol. 2023.

29. Pala F, Corsino C, Calzoni E, Villa A, Pittaluga S, Palchaudhuri R, et al. Transplantation after CD45-ADC corrects Rag1 immunodeficiency in congenic and haploidentical settings. J Allergy Clin Immunol. 2023.

30. Kwon HS, Logan AC, Chhabra A, Pang WW, Czechowicz A, Tate K, et al. Anti-human CD117 antibody-mediated bone marrow niche clearance in nonhuman primates and humanized NSG mice. Blood. 2019;133:2104-8.

31. Davies EG, Cheung M, Gilmour K, Maimaris J, Curry J, Furmanski A, et al. Thymus transplantation for complete DiGeorge syndrome: European experience. J Allergy Clin Immunol. 2017;140:1660-70.e16.

32. Gardner CL, Pavel-Dinu M, Dobbs K, Bosticardo M, Reardon PK, Lack J, et al. Gene editing rescues in vitro T cell development of RAG2-deficient induced pluripotent stem cells in an Artificial Thymic Organoid System. J Clin Immunol. 2021;41:852-62.

33. McAuley GE, Yiu G, Chang PC, Newby GA, Campo-Fernandez B, Fitz-Gibbon ST, et al. Human T cell generation is restored in CD3delta severe combined immunodeficiency through adenine base editing. Cell. 2023;186:1398-416.e23.