The Ever-Increasing Array of Novel Inborn Errors of Immunity: an Interim Update by the IUIS Committee

Stuart G. Tangye 1,2 · Waleed Al-Herz 3 · Aziz Bousfiha 4 · Charlotte Cunningham-Rundles 5 · Jose Luis Franco 6 · Steven M Holland 7 · Christoph Klein 8 · Tomohiro Morio 9 · Eric Oksenhendler 10 · Capucine Picard 11,12 · Anne Puel 13,14 · Jennifer Puck 15 · Mikko R. J. Seppänen 16 · Raz Somech 17 · Helen C Su 7 · Kathleen E. Sullivan 18 · Troy R. Torgerson 19 · Isabelle Meyts 20

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Abstract
The most recent updated classification of inborn errors of immunity/primary immunodeficiencies, compiled by the International Union of Immunological Societies Expert Committee, was published in January 2020. Within days of completing this report, it was already out of date, evidenced by the frequent publication of genetic variants proposed to cause novel inborn errors of immunity. As the next formal report from the IUIS Expert Committee will not be published until 2022, we felt it important to provide the community with a brief update of recent contributions to the field of inborn errors of immunity. Herein, we highlight studies that have identified 26 additional monogenic gene defects that reach the threshold to represent novel causes of immune defects.

Keywords Inborn errors of immunity · immune dysregulation · primary immunodeficiencies · autoinflammatory disorders

Introduction

Inborn errors of immunity (IEI) are generally considered to result from monogenic germline defects that manifest as increased susceptibility to severe and/or recurrent infectious diseases, autoimmune or autoinflammatory conditions, atopic manifestations, and hematopoietic or solid tissue malignancies [1]. Over the past decade, the discovery of new IEIs has been occurring at an impressive rate. Indeed, the 2011 biennial update published by the IUIS Committee update listed 191 IEIs; this number increased to 430 in the 2019 update [2, 3]. This near-exponential increase in gene discovery is being driven by the accessibility and affordability of next-generation sequencing, and the efficient application of these technologies to elucidate the molecular etiology of unsolved cases of IEIs that are likely to result from single-gene defects [4].

Over the last 12 months, we have witnessed the ongoing rapid identification, and occasionally detailed molecular, biochemical, and cellular characterization, of genetic variants that cause, or are at least associated with, human diseases impacting host defense or immune regulation. Here, we will summarize reports on variants detected in 26 genes which we consider represent novel IEI (Table 1). Many additional genetic variants have been reported recently. However, those listed here have been adjudicated by the IUIS Committee to meet the strict criteria to be considered disease-causing [5, 7]. These criteria include:

1. The patient’s candidate genotype is monogenic and must not occur in individuals without the clinical phenotype;
2. Experimental studies must indicate the genetic variant impairs, destroys, or alters expression or function of the gene product;
3. The causal relationship between the candidate genotype and the clinical phenotype must be confirmed via a relevant cellular phenotype, including—where possible—rescue of a functional defect by reconstitution with the wild-type gene, or via a relevant animal phenotype [5, 7].

We also considered (i) the numbers of individuals affected by the novel variants, (ii) sufficient justification for excluding...
alternative candidate gene variants identified in single cases especially in situations of consanguinity with recessive disease, (iii) the depth of the clinical descriptions of affected individuals, and (iv) the level of immune and mechanistic characterization.

**Novel Causes of Inborn Errors of Immunity**

Currently, inborn errors of immunity are listed in 10 tables: Immunodeficiencies affecting cellular and humoral immunity (Table I), Combined immunodeficiencies (CID) with syndromic features (Table II), Predominantly antibody deficiencies (Table III), Diseases of immune dysregulation (Table IV), Congenital defects of phagocytes (Table V), Defects in intrinsic and innate immunity (Table VI), Autoinflammatory diseases (Table VII), Complement deficiencies (Table VIII), Bone Marrow failure (Table IX), and Phenocopies of inborn errors of immunity (Table X). Several of these tables are further partitioned into various subtables (e.g., Table I is split into Subtable 1 [T'B' Severe Combined Immune Deficiency (SCID)], Subtable 2 [T'B' SCID] and Subtable 3 [CID, generally less profound than SCID]) [2, 3].

Recently-reported gene defects have been found for most categories of inborn errors of immunity, including novel causes of:

- SCID (PAXI [5, 6], SLP76 [7]);
- CID (MCM10 [8], IL6ST [9–11]);
- Predominantly antibody deficiencies (FNIP1 [14, 15], PIK3CG [16, 17], CTNMBL1 [18], TNFSF13 [19]);
- Autoinflammatory diseases (SOCS1 [20–22], TET2 [23], CEBPE [24], CDC42 [33–39], LSM11, RNU7-1 [32], STAT2 [40, 41], RIPK1 [42, 43], NCKAPIL [44–46], UBA1 (somatic mutations) [47]); and
- Susceptibility to infection with specific pathogens (MAPK8 [31]; TBX21 [25], IFNG [26], NOS2 [28], SNORA31 [29], ATG4A, MAP1LC3B2 [30]) (Table 1).

Notably, several of these genes are already included in previous IUIS updates, namely IL6ST, STAT2, CEBPE, and RIPK1 [2, 3]. However, they are listed here because the variant identified is pathogenic via a distinct mechanism and/or different mode of inheritance; i.e., autosomal recessive (AR) vs autosomal dominant for IL6ST [9] or RIPK1 [42, 43], partial deficiency vs complete deficiency for IL6ST [10, 11], or AR loss of function vs AR gain of function for CEBPE [24] or STAT2 [40, 41]. Furthermore, the GOF variants reported for CEBPE appear to represent the first described germline neomorphic mutation in inborn errors of immunity where the variant allele has completely novel functions not seen for the wild type gene [24]. Thus, these findings underscore the importance of appropriately interpreting genetic variants identified by next-generation sequencing, not discarding variants of unknown significance simply because they do not match the expected zygosity or clinical phenotype of previously reported studies, and to rigorously validate the impact of novel variants on the function of the encoded protein.

**Joining the Dots with Discoveries of Novel Inborn Errors of Immunity**

Many known inborn errors of immunity impact a defined signaling pathway such that mutations in components of these same pathways can represent clinical phenocopies of diseases causes by distinct genetic variants (genetic heterogeneity). In other words, physiological homogeneity can be identified for many genotypes underlying a given phenotype. Classic examples of this are Mendelian susceptibility to mycobacterial disease (MSMD), which results from impaired IFNγ-mediated immunity following exposure to mycobacterial species [58], and herpes simplex virus encephalitis (HSE) resulting from impaired TLR3-mediated anti-HSV1 immunity [59, 60]. Thus, variants in genes affecting the production of IFNγ (e.g., IL12RB1, IL12RB2, IL23R, TYK2, IKBKGA, SPL2A, IRF8) or cellular responses to IFNγ (e.g., IFNγR1, IFNγR2, STAT1, JAK1) result in MSMD in otherwise healthy individuals [58]. Similarly, inactivating mutations in signaling components of the TLR3 signaling pathway (TLR3, UNC93B, TRIF, TRAF3, TBK1, IRF3) underlie HSE due to impaired type 1 IFN-mediated central nervous system (CNS) intrinsic immunity against HSV1 [59, 60].

Recent discoveries have further linked common clinical phenotypes with unique genotypes that converge in a shared pathway. Thus, the non-redundant role of IFNγ-mediated immunity in host defense against mycobacterial infection [58] has been definitively established by the identification of individuals with inactivating bi-allelic mutations in not only IFNG itself [26] but also TBX21 [25], the transcription factor that regulates expression and production of IFNγ. Interestingly, variants in the small nucleolar RNA SNORA31 predispose affected individuals to HSE. Mechanistically, patient’s iPSC-derived cortical neurons were
found to be highly susceptible to HSV-1 infection in vitro, and this could be restored by exogenous IFNβ [29, 60]. However, responses of these cells to TLR3 and IFNβ, but not HSV1, are intact, revealing that SNORA31 functions to regulate cell-intrinsic immunity to HSV-1 by a mechanism independent of TLR3 signaling [29, 60]. The discovery of individuals with SNORA31 variants will facilitate further understanding of CNS-intrinsic host defense.

The discoveries of individuals with complete gp130-deficiency due to null/nonsense bi-allelic mutations of IL6ST [11], or pathogenic dominant-negative heterozygous variants of IL6ST [9], and a phenotype of eczema, hyper-IgE, and eosinophilia, likely explain these features of autosomal dominant hyper-IgE syndrome due to STAT3 negative dominance [61] and further highlight the role of IL-6 signaling in restraining atopic and allergic responses. Furthermore, the lack of mucocutaneous candidiasis in patients with impaired signaling via receptors for IL-6 (IL6R, IL6ST mutations [9, 11, 50, 62, 63]; anti-IL-6 autoantibodies [64]), IL-23 (biallelic IL23R variants) [65] or IL-21 (biallelic IL21 or IL21R variants) [66] argues that individually these cytokines are not required for the STAT3-mediated generation of human Th17 cells and host defense against fungal infections. Rather, the combinatorial defect of impaired STAT3 signaling downstream of these receptors explains chronic mucocutaneous candidiasis in an individual with dominant-negative STAT3 mutations. These findings again reveal the capacity for inborn errors of immunity to provide convincing evidence for basic immunological concepts. Indeed, this is further exemplified by the discovery that variants of ATG4A or MAP1LC3B2 cause recurrent HSV2 infection of the CNS, thereby establishing hitherto non-redundant functions of the autophagy pathway in non-hematopoietic cell-mediated intrinsic anti-viral immune responses [30].

**SARS-CoV2 and Inborn Errors of Immunity**

The COVID19 pandemic of 2020 has clearly changed the world in many ways. It has also yielded opportunities to understand host requirements for immunity against SARS-CoV2 infection. A recent study of ~650 individuals who developed severe COVID-19 found that ~3.5% of patients harbored germline loss-of-function variants in genes previously found to be important for host defense against influenza or other viral infections (e.g., bi-allelic loss of function mutations of IRF7 or IFNAR1, heterozygous mutations in TLR3, TICAM1, TBK1, or IRF3) [67] due to the key role of these genes in the type 1 IFN signaling pathway [59, 68]. An accompanying study found that, strikingly, ~10% of patients with severe COVID-19 have high levels of neutralizing autoantibodies (autoAbs) against type 1 IFNs in their serum [48]. The impact of these autoAbs was evidenced by the inability to detect IFN in serum from these patients, and their capacity to prevent anti-viral immune responses in vitro [48] (Table 1). These studies defined a crucial and non-redundant role for type 1 IFNs in immune control of SARS-CoV2 infection, and thus prevention of severe COVID-19. Furthermore, they also established that autoAbs against type 1 IFN phenocopy an inborn error of immunity, as previously determined for autoAbs against IFNγ and susceptibility to mycobacterial disease, anti-Th17 cytokine (IL-17A, IL-17F, IL-22) autoAbs in individuals with chronic mucocutaneous candidiasis, or pyogenic infections due to anti-IL-6 autoAbs [64, 69].

**Conclusions**

Discoveries over the past 12 months in the field of inborn errors of immunity have further identified non-redundant functions of key genes in human immune cell development, host defense, and immune regulation. In some cases, these functions go well beyond what may have been expected or anticipated based on animal models (e.g., TBX21 [25]). They have also already highlighted the heterogenous phenotypes that can result from variants in the same gene (e.g., CDC42 [33–39, 52]), indicated that significant diseases can arise from mono-allelic or bi-allelic loss of function (IL6ST [9], RIPK1 [42, 43]) or bi-allelic loss- or gain-of-function (CEBPE [24], STAT2 [40, 41]) variants in the same gene, or from autoAb phenocopies of monogenic lesions (e.g., COVID19 and anti-IFN Abs) [48], and identified novel somatic mutations as pathogenic causes of immune disorders (UBA1) [47]. Importantly, they have also provided opportunities for therapeutic interventions, such as JAK inhibitors to treat STAT2 gain of function [40, 41] or SOCS1 deficiency [22], IFNγ to treat mycobacterial disease [25, 26], or early IFN-β or IFN-α2a treatment of SARS-CoV2 infection in COVID-19 patients with autoantibodies against IFN-α or IFN-ω [67] or impaired type 1 IFN responses [70]. This snapshot of genetic discoveries underpinning human immune disorders further highlights the critical contributions of inborn errors of immunity to our broader understanding of basic, translational, and clinical immunology.
### Table 1  Newly validated inborn errors of immunity

| Genetic defect | Inheritance/mechanisms | T/NK cells | B cells | Ig levels | Clinical features, cellular defects, and evidence of variant pathogenicity | References |
|----------------|-------------------------|------------|---------|-----------|---------------------------------------------------------------------|------------|
| **PAX1** (8 patients, 3 families; 2 papers with overlapping patients) | AR (LOF) | T B+NK* SCID | Normal | ~Normal IgM, low IgA, normal to ↑ IgE, | Ommen’s-like syndrome (erythroderma, lymphocytosis, eosinophilia, ↓ proliferation to PHA, severe/recurrent infections), No thymus, T cell deficiency not corrected by HSCT despite donor chimerism, Also: otofaciocervical syndrome type 2 (OTFCS2) | Table 1 Subtable 1 [5, 6] |
| **SLP76** (1 patient) | AR (LOF) | T cells reduced, ↓ CD4+, ↑ CD8+ T cell proportions | Normal numbers but ↓ class-switched memory and transitional B cells, ↓ naïve and immature B cells | High IgM, low IgA | Combined immunodeficiency, Early-onset skin abscesses, rash recurrent infections, autoimmunity, Neutrophil dysfunction, platelets dysfunction, ↓ T cell proliferation to PHA, anti-CD3/CD28 stimulation, partially restored by IL-2, ↓ NK cell degranulation, ↓ Actin polymerization | Table 1 Subtable 1 [7] |
| **MCM10** (1 patient) | AR (LOF) | Mild lymphopenia | ↓ B cells | slightly ↓ IgG, normal IgM/A | Severe (fatal) CMV infection, HLH-like (based on biomarkers, not clinical features), Phenocopies GINS1 and MCM4 deficiencies, ↓ NK function | Table 2 Subtable 2 [8] |
| **IL6ST** (gp130; 12 patients, 8 families) | AD (DN) | Normal T cell numbers | Normal numbers of B cells, low memory B cell proportions | Normal low IgG, A, Normal IgM, Hyper IgE; vaccine IgG normal | HIES – STAT3-like; Dermatitis/eczema, eosinophilia, recurrent skin infections, pneumonia, bronchiectasis, pneumatoceles with severe secondary pulmonary aspergillosis, connective tissue defects (scoliosis, face, joints, fractures, palate, tooth retention), Phenocopies aspects of IL6R and IL11R deficiencies (due to unresponsiveness to these cytokines) | Table 2 Subtable 5 [9] |
Table 1 (continued)

| Gene   | Mode of Inheritance | Phenotype                                                                                                                                          |
|--------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| *IL6ST* (complete deficiency) | AR (LOF) | ND (death in utero or in neonatal period occurred for most affected individuals) LOF and DN alleles shown by overexpression in GP130 deficient HEK293T cells; impaired GP130/STAT3 signaling (mostly downstream of IL-6) in patients' fibroblasts and leukocytes; fatal Stuve-Wiedemann-like syndrome; skeletal dysplasia, lung dysfunction, renal abnormalities, thrombocytopenia, dermatitis, eczema; defective acute phase response; complete unresponsiveness to IL-6 family cytokines Validation: complete LOE (for one allele) and LOF for two alleles tested by overexpression in GP130 deficient HEK293T to all cytokines tested of the IL-6 family. Effects of variants well-characterized, including a partial rescue of patient amniocytes. |
| *FN1P1* (6 patients; 5 families) | AR (LOF) | Mild T cell lymphocytosis B cell lymphopenia (absent/low; BM block [few immature B cells]) agamma/ hypogammaglobulinemia Early onset recurrent infections (sinopulmonary) Bronchiectasis Congenital heart defects (e.g., hypertrophic cardiomyopathy) Variable neutropenia (severe or intermittent) Crohn disease (one patient) Developmental delay Increased AMPK activity Validation: almost recapitulates the mouse model; Cytopenia lymphopenia, eosinophilia, lymphadenopathy, splenomegaly, recurrent infections HLH-like; ↑ inflammatory markers |
| *PIK3CG* (2 patients; 2 families) | AR (LOF) | ↓ T cells Normal CD4, ↓ Treg, ↓ CD8 Normal but ↓ memory B cells Hypogamma Intact vaccine responses Cytopenia/lymphopenia, eosinophilia, lymphadenopathy, splenomegaly, recurrent infections HLH-like; ↑ inflammatory markers Validation: ↓ T cell proliferation, activation in vitro Cellular defects recapitulated in *PIK3CG* targeted Jurkat T cell line and *Pik3cg* ko mice CVID, autoimmune cytopenias, hypogamma, recurrent infections, hyperplastic GC's; (mutation reduces binding of *CTNNBL1* to AID, resulting in less nuclear translocation of AID) Validation: detailed functional analysis of *CTNNBL1* variant in EBV B lines, and engineered RAMOS cell lines; mutant allele reduces the binding of *CTNNBL1* to AID, with impaired nuclear translocation of AID; defective SHM rescued in mutant Ramos cells by WT *CTNNBL1* CVID, chronic but mild infections Validation: LOE and LOF allele, |
| *TNFSF13B* (April; 1 patient) | AR (LOF) | Normal T/NK cells Normal total B cell counts, Hypogamma | CVID, chronic but mild infections Validation: LOE and LOF allele, |
|        |                     | Table 2 Subtable 5 Table 3 Subtable 1 Table 3 Subtable 2 Table 3 Subtable 3 |
Table 1 (continued)

| SOCS1 (15 patients; 10 families) | AD (by haploinsufficiency) | Predominant naïve B cells, ↓ sw memory, ↑ IgM+ marginal zone B cells, ↓ blood plasmablasts | Functional analysis of the variant in PBMCs and overexpression; Impaired function of iPSC-moDC in promoting B cell differentiation could be rescued with exogenous APRIL; Recurrent bacterial infections, Severe multisystemic autoimmunity (flared in context of infection-induced inflammation), ITP, AIHA, SLE, GN, hepatosplenomegaly, psoriasis, arthritis, thyroiditis, hepatitis; Evans syndrome; 1 patient developed COVID19/MIS-C; neutropenia, lymphopenia; incomplete penetrance | Table 4 Subtable 4 [20–22] |
|---------------------------------|---------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------|
| TET2 (3 patients, 2 families)   | AR (LOF)                  | ↑ DN T cells, ↓ Th1, Th17, Th2 cells, ↓ Memory B cells, Impaired B cell differentiation in vitro to plasma cells | Variable (hyper-/-hypogamma, ↓ response to pneumococcal vaccine | Table 4 Subtable 7 [23] |
| CEBPE (3 patients, 1 family)    | AR (GOF)                  | Mild lymphopenia, ↓ naïve, ↑ TEMRA cells | Normal | Table 5 Subtable 2 [24] |
| TBX21 (T-bet; 1 patient)        | AR (LOF)                  | Normal % total CD4 and CD8 T cells, naïve and memory subsets, low frequencies of NK cells | Normal | Table 6 Subtable 1 [25] |
| Subtable 1 | Subtable 2 | Subtable 3 | Subtable 4 |
|------------|------------|------------|------------|
| **IFNG** (2 patients [cousins]) | AR (LOF) | Normal frequencies of T and NK cells; ↑ proportions of naive CD4+ and CD8+ T cells; ↓ frequency of invariant iNKT | • Normal B cell frequencies; ↓ memory B cells (↓ IgA+ / IgM+, ↑ IgG+ memory B cells) | • Normal MSMD/BCG-osis | Table 6 Subtable 1 [26] |
|          |           | Normal     | Normal     | No IFN-γ producing cells | Validation |
|          |           | Normal     | Normal     | Validation: LOE and LOF allele | LOE and LOF allele |
| NOS2 (1 patient) | AR | ↓ CD4+ T cells; ↓ NK cells (mostly all immature cells) | B cells ND (specific Ab levels normal) | • Severe susceptibility to CMV-induced disease; fatal | Validation: Confirmed functional defect in transfected cells; truncated NOS2 failed to induce nitrous oxide |
|          |           | Normal     | Normal     | • Pneumocystis pneumonia secondary to CMV | Recapitulates susceptibility of Nos2 deficient mice to murine CMV infection [27] (these mice are also susceptible to numerous other pathogens) |
|          |           | Normal     | Normal     | • Apparent intact responses to infection with other herpes viruses (EBV, VZV, HSV) | Validation: Susceptibility of human pluripotent stem cell (hPSC)–derived cortical neurons from patients or hPSC-derived neurons from healthy donors but engineered to express variant SNORA31 to HSV1 infection, corrected by exogenous IFN-β |
| SNORA31 (5 patients, unrelated) | AD | Normal | Normal | Seropositive for IgG against many viruses | Table 6 Subtable 3 [28] |
|          |           | Normal | Normal | Validation: Susceptibility of human pluripotent stem cell (hPSC)–derived cortical neurons from patients or hPSC-derived neurons from healthy donors but engineered to express variant SNORA31 to HSV1 infection, corrected by exogenous IFN-β |
|            |           | Normal | Normal | Incomplete penetrance |
| ATG4A (1 patient) | AD | Normal | Normal | Normal | Normal | Table 6 Subtable 4 [29] |
| MAP1LC3B2 (1 patient) | Normal | Normal | Normal | Normal | Table 6 Subtable 4 [30] |
|          |           | Normal | Normal | Validation: Impaired HSV2-induced autophagy → increased viral replication and apoptosis of patient fibroblasts |
|          |           | Normal | Normal | These defects were rescued by introduction of WT ATG4 or LC3B2 into patient fibroblasts |
### Table 1 (continued)

| Gene | Family/Oncogenicity | Clinical Findings | Immunological Findings | Validation |
|------|---------------------|-------------------|------------------------|------------|
| **MAPK8** | (3 patients, 1 family) | AD (haploinsufficiency) | • Normal total T cells, CD4+ and CD8+ T subsets, NK cells | • Normal total B cells and subsets | • Chronic mucocutaneous candidiasis (CMC) |
|          |                     |                   | • ↓ Th17 cells | • Normal | • Connective tissue disorder (similar to Ehlers-Danlos syndrome) |
|          |                     |                   | • ↓ Th17 cells ex vivo, in vitro |       | • ↓ Responses of fibroblasts to IL-17A, IL-17F |
|          |                     |                   | • ↓ c-Jun/ATF-2-dependent TGF β signaling |       | • Validation |
|          |                     |                   | • MAPK8 variant LOE in HEK293 T, heterozygous patients’ cells |       | • Defective responses of fibroblasts restored by WT MAPK8 |
|          |                     |                   | • Not reported |       | • Aicardi-Goutieres syndrome (type 1 IFN-opathy) |
| **LSM11** | (2 siblings, 1 family) | AR (LOF) | • Normal/decreased T cell numbers, normal %CD4/CD8 but skewed differentiation | • Variable (↑↓) IgM, G, A, E | • Neonatal onset: pancytopenia, fever, rash, hepatosplenomegaly, systemic inflammation, myelofibrosis/proliferation, HLH, multisystemic inflammatory disease |
|          |                     |                   | • Total B cell frequencies within age-matched controls’ ranges |       | • ↑ serum levels of IL1, IL18, IFN-γ, ferritin, sCD25, CRP etc. |
|          |                     |                   | • ↓ transitional and naïve B cells %’s |       | • Recurrent GIT/RT infection; |
|          |                     |                   |                  |       | • Neurodevelopmental delay, FTT |
|          |                     |                   |                  |       | • Mutation affects actin function; |
|          |                     |                   |                  |       | • Treated with Anakinra/ IFN-γ mAb |
| **RNU7-1** | (16 patients, 11 kindreds) | AD | • Low frequency of NK, ↑ frequency of T cells (esp naïve), normal NK degranulation | • Low/normal | • Severe fatal early-onset autoinflammation (skin ulceration, fever, seizures, intracranial calcification, multiorgan dysfunction, abnormal neurodevelopment; phenocopy of USP18 deficiency) |
|          |                     |                   | • Total B cell frequencies within age-matched controls’ ranges |       | • ↑ serum IFN-α, IL6, TNFα |
|          |                     |                   | • ↓ transitional and naïve B cells %’s |       | • IFN-opathy gene signature (impaired regulation of late cellular responses to type 1 IFN), |
| **STAT2** | (GOF, 3 patients; all deceased; 2 additional deceased sibs but not genotyped; 2 unrelated families) | AR (GOF) | • Normal total T cells, CD4+ and CD8+ T subsets, NK cells | • Normal total B cells and subsets | • Study of the mutant STAT2 alleles in STAT2 deficient human cell line, and patient’s immortalized fibroblasts |
|          |                     |                   | • ↓ Th17 cells | • Normal | • Validation |
|          |                     |                   | • ↓ Th17 cells ex vivo, in vitro |       | |
### Table 1 (continued)

| Condition | Inheritance | Characteristics |
|-----------|-------------|-----------------|
| **RIPK1** (12 patients; 5 families, 2 papers) | AD | - Normal T and NK cell numbers  
- Low/normal CD4⁺ T cells  
- Normal/hi CD8⁺ T cells  
- ↑ DN T cells  
- Patient cells hyper-sensitive to IFN-α → prolonged JAK/STAT signaling/transcriptional activation  
- Biochemical confirmation that mutant allele is GOF in homozygous, but not heterozygous, combination  
- Impaired interaction of GOF STAT2 protein with USP18, a negative regulator of type I IFN responses  
- Autoinflamm disorder: regular/prolonged fevers, lymphadenopathy, spleno/hepatomegaly, ulcers, arthralgia, GI features,  
- ↑ inflam markers, ↑ pro-inflamm cytokines/gene signature;  
- Responsive to Tocilizumab (not IL1/TNF blockade) |
| **NCKAP1L** (9 patients; 7 families, 3 papers) | AR (LOF) | - Normal T cell numbers  
- ↑ TCM, exhausted cells;  
- Possibly immature NK cells but intact function  
- Normal B cells and naïve/memory subsets  
- ↑ CD21<sup>lo</sup> cells  
- Recurrent URTI, skin rashes/abscesses, ulcers,  
- Anti dsDNA Abs, SLE-like, lymphadenopathy, fever, HLH-like  
- FTT  
- Immunodeficiency coupled with atopy, lymphoproliferation, hyperinflammation, and cytokine overproduction (↑ Th1)  
- ↓ T cell proliferation, cytoskeletal defects;  
- Late adulthood onset treatment-refractory inflammatory syndrome |
| **UBA1** (25 patients) | XL (somatic LOF mutations) | - ↓ Peripheral lymphocyte counts  
- Loss of immature B cells, nonclassical and intermediate monocyte populations  
- ↓ Peripheral lymphocyte counts  
- Loss of immature B cells, nonclassical and intermediate monocyte populations  
- Patient cells hyper-sensitive to IFN-α → prolonged JAK/STAT signaling/transcriptional activation  
- Biochemical confirmation that mutant allele is GOF in homozygous, but not heterozygous, combination  
- Impaired interaction of GOF STAT2 protein with USP18, a negative regulator of type I IFN responses  
- Autoinflamm disorder: regular/prolonged fevers, lymphadenopathy, spleno/hepatomegaly, ulcers, arthralgia, GI features,  
- ↑ inflam markers, ↑ pro-inflamm cytokines/gene signature;  
- Responsive to Tocilizumab (not IL1/TNF blockade) |

| Validation: | - Overexpression of mutant allele favored the production of a catalytically deficient UBA1 | |
Table 1 (continued)

| Disease                      | Mechanisms of disease pathogenesis                                                                 | Associated/clinical features                                                                 | Table | Refs   |
|------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------|--------|
| Severe COVID-19              | • High levels of neutralizing autoAbs against type 1 IFNs (primarily IFNα, IFNω)                   | • Severe, life-threatening infection with SARS-CoV-2                                         | Table 10 | [48]   |

**Novel phenocopies of inborn errors of immunity**

| Disease                      | Mechanisms of disease pathogenesis                                                                 | Associated/clinical features                                                                 | Table | Refs   |
|------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------|--------|
| Severe COVID-19              | • High levels of neutralizing autoAbs against type 1 IFNs (primarily IFNα, IFNω)                   | • Severe, life-threatening infection with SARS-CoV-2                                         | Table 10 | [48]   |

**Abbreviations:** AR, autosomal recessive; AD, autosomal dominant; AID, activation-induced cytidine deaminase; CSR, class switch recombination; SHM, somatic hypermutation; MDS, myelodysplastic syndrome; LOE, loss of expression; LOF, loss of function; GOF, gain of function; DN, dominant negative; MSMD, Mendelian susceptibility to mycobacterial disease; HLH, hemophagocytic lymphohistiocytosis; FTT, failure to thrive; hPSC, human pluripotent stem cells; iPSC, induced pluripotent stem cells; CMV, cytomegalovirus

- Not all Tables in the 2020 classifications [2, 3] are listed in the “Table” column because not all Tables are represented by the new variants detailed above
- Mutations in PAX1 previously reported to cause OTFCFS2 (but CID/SCID not reported) [49]
- Variants in IL6ST have been previously listed to cause an IEI due to recessive partial LOF alleles [50]
- Dominant-negative mutations in IL6ST all target the intracellular domain of gp130, truncating the STAT3 binding sites as well as recycling motif, leading to sustained expression of a dead receptor (as opposed to recessive alleles, when detected in heterozygous carriers are benign)
- Fnip1 ko mice also previously reported [12, 13]; humans very similar
- Variants in CEBPE have been previously listed to cause an IEI due to recessive LOF alleles [51]
- Mutations in CDC42 previously identified in individuals with neurodevelopmental delay (Takenouchi-Kosaki syndrome) [52]; in these patients with autoinflammation and CDC42 mutations no such features were noted, except mild facial dysmorphism in some [33–39]
- Variants in STAT2 have been previously listed to cause an IEI due to recessive LOF alleles [53, 54]
- The same amino acid was found to be affected (R148Q/W) for both families affected by STAT2 GOF [53, 54]
- Variants in RIPK1 have been previously listed to cause an IEI due to recessive LOF alleles [55, 56]; the heterozygous dominant mutations in RIPK1 reported here all affect the D324 amino acid residue that is important for cleavage
Authors Contribution SGT wrote the drafts of the manuscript, prepared the table, and revised the original manuscripts for resubmission. All co-authors contributed to and edited drafts of the original and revised manuscripts and table, and approved the final submitted version.

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Data Availability Not applicable.

Declarations

Ethics Approval This work is a review of recently-reported genetic variants that represent novel inborn errors of immunity. No human research studies were performed in order to produce this review. Thus, no approvals by appropriate institutional review boards or human research ethics committees were required to undertake the preparation of this report.

Consent to Participate Not applicable as this is a review of recently-reported genetic variants.

Consent for Publication The authors consent to publish the content of this review. However, as noted above, as this is a review of recently-reported genetic variants that represent novel inborn errors of immunity, we did not require consent to publish from participants.

Conflict of Interest The authors declare that they have no conflict of interest.

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Affiliations

Stuart G. Tangye 1,2 · Waleed Al-Herz 3 · Aziz Bousfiha 4 · Charlotte Cunningham-Rundles 5 · Jose Luis Franco 6 · Steven M Holland 7 · Christoph Klein 8 · Tomohiro Morio 9 · Eric Oksenhendler 10 · Capucine Picard 11,12 · Anne Puel 13,14 · Jennifer Puck 15 · Mikko R. J. Seppänen 16 · Raz Somech 17 · Helen C Su 7 · Kathleen E. Sullivan 18 · Troy R. Torgerson 19 · Isabelle Meyts 20

1 Garvan Institute of Medical Research, Darlinghurst, Sydney, New South Wales 2010, Australia
2 Faculty of Medicine, St Vincent’s Clinical School, UNSW Sydney, Sydney, NSW, Australia
3 Department of Pediatrics, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait
4 Laboratoire d’Immunologie Clinique, d’Inflammation et d’Allergy LICIA Clinical Immunology Unit, Casablanca Children’s Hospital, Ibn Rochd Medical School, King Hassan II University, Casablanca, Morocco
5 Departments of Medicine and Pediatrics, Mount Sinai School of Medicine, New York, NY, USA
6 Grupo de Inmunodeficiencias Primarias, Facultad de Medicina, Universidad de Antioquia UdeA, Medellin, Colombia
7 Laboratory of Clinical Immunology & Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
8 Dr von Hauner Childrens Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
9 Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, Tokyo, Japan
10 Department of Clinical Immunology, Hôpital Saint-Louis, APHP, University Paris Diderot, Sorbonne Paris Cité, Paris, France
11 Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children, APHP, Paris, France
12 Laboratory of Lymphocyte Activation and Susceptibility to EBV, INSERM UMR1163, Imagine Institute, Necker Hospital for Sick Children, Paris University, Paris, France
13 Laboratory of Human Genetics of Infectious Diseases, INSERM U1163, Necker Hospital, 75015 Paris, France
14 Imagine Institute, University of Paris, 75015 Paris, France
15 Department of Pediatrics, University of California San Francisco and UCSF Benioff Children’s Hospital, San Francisco, CA, USA
16 Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center and Rare Diseases Center, Childrens Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
17 Pediatric Department and Immunology Unit, Sheba Medical Center, Tel Aviv, Israel
18 Division of Allergy Immunology, Department of Pediatrics, Childrens Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
19 Allen Institute for Immunology, Seattle, WA, USA
20 Department of Immunology and Microbiology, Laboratory for Inborn Errors of Immunity, Department of Pediatrics, University Hospitals Leuven and KU Leuven, 3000 Leuven, Belgium