



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

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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 Within days of completing this report, it was already out of date, evidenced by the frequent publication of genetic variants proposed to cause novel inborn errors of immunity. As the next formal report from the IUIS Expert Committee will not be published until 2022, we felt it important to provide the community with a brief update of recent contributions to the field of inborn errors of immunity.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 [57]. 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 [57].

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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 (*PAX1* [5, 6], *SLP76* [7]);
- CID (*MCM10* [8], *IL6ST* [9–11]);
- Predominantly antibody deficiencies (*FNIP1* [14, 15], *PIK3CG* [16, 17], *CTNBL1* [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], *NCKAP1L* [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 caused 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 $IFN\gamma$ -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 $IFN\gamma$ (e.g., *IL12RB1*, *IL12RB2*, *IL23R*, *TYK2*, *IKBK1*, *SPPL2A*, *IRF8*) or cellular responses to $IFN\gamma$ (e.g., *IFNGR1*, *IFNGR2*, *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 $IFN\gamma$ -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 $IFN\gamma$.

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 IFN β [29, 60]. However, responses of these cells to TLR3 and IFN β , 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 IFN γ 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 heterogeneous 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], IFN γ to treat mycobacterial disease [25, 26], or early IFN- β or IFN- α 2a 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

Novel gene defects underlying IEI—2020		Inheritance/mechanisms		T/NK cells	B cells	Ig levels	Clinical features, cellular defects, and evidence of variant pathogenicity	Table (for classification) ^{1,2,3)}	Refs
PAX1 (8 patients, 3 families; 2 papers with overlapping patients)	AR (LOF)	AR (LOF)	<ul style="list-style-type: none"> T cells reduced, ↓ CD4+, ↑ CD8+ T cell proportions Low naive, ↑ T_{CM} CD4+ T cells; CD8+ T cell mostly clonally expanded T_{EMRA} Low TREGs NK normal numbers 	<ul style="list-style-type: none"> Normal numbers but ↓ class-switched memory and transitional B cells, ↑ naive and immature B cells 	<ul style="list-style-type: none"> ~Normal IgM, low IgA, normal to ↑ IgE, 	<ul style="list-style-type: none"> Omenn'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 (OIFCS2) 	Table 1 Subtable 1	[5, 6]	
									<p>Validation</p> <ul style="list-style-type: none"> Reporter assays established hypomorphic LOF of mutant alleles Patients' derived iPSCs differentiated to thymic epithelial cells demonstrated abnormalities in thymic epithelial progenitors, consistent with failure of HSCT to reconstitute T cells Similar to mouse model 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 <p>Validation</p> <ul style="list-style-type: none"> Generation of SLP76-deficient Jurkat T cells; expressing WT or mutant <i>SLP76</i> allele, mimicking patient cellular phenotypes; Partial rescue of some of the functional defects by expression of WT <i>SLP76</i>
MCM10 (1 patient)	AR (LOF)	AR (LOF)	<ul style="list-style-type: none"> Mild lymphopenia ↓ T_{CM}, T_{EM} cells ↓↓↓ NK cells (↑ CD56^{bright}, nearly absent CD56^{dim} mature NK) 	<ul style="list-style-type: none"> ↓ B cells 	<ul style="list-style-type: none"> slightly ↓ IgG, normal IgM/A 	<ul style="list-style-type: none"> Phenocopies <i>GINS1</i> and <i>MCM4</i> deficiencies ↓ NK function <p>Validation</p> <ul style="list-style-type: none"> Detailed functional analysis of <i>MCM10</i> variant in primary fibroblasts, transfectants, iPSC, and CRISPR/Cas9-gene-edited NK92 human NK cell line Assessed mutant allele on NK cell development in humanized mice reconstituted with CD34⁺ HSC generated from the patients or healthy donor iPSCs 	Table 2 Subtable 2	[8]	
IL6ST (gp130; 12 patients, 8 families)	AD (DN)	AD (DN)	<ul style="list-style-type: none"> Normal T cell numbers ↑ naive CD4 and CD8 T cell proportions ↓ T_{CM} CD4+ and CD8+ T cells and T_{EM} CD8 T cells; ↓ MAIT, Tfh cells, ↑ Th2, Low to normal NK cell counts 	<ul style="list-style-type: none"> Normal numbers of B cells, low memory B cell proportions ↑ naive and immature B cells 	<ul style="list-style-type: none"> Normal/low IgG, A, Normal IgM, Hyper IgE, vaccine IgG normal 	<ul style="list-style-type: none"> 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)

<i>IL6ST</i> (complete deficiency; 6 patients, 4 families)	AR (LOF)	ND (death in utero or in neonatal period occurred for most affected individuals)			<p>Validation</p> <ul style="list-style-type: none"> • 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 <p>Table 2 Subtable 5</p> <p>[10, 11]</p>
<i>FN1P1</i> (6 patients; 5 families)	AR (LOF)	Mild T cell lymphocytosis	B cell lymphopenia (absent/low; BM block [few immature B cells])	agamma/hypogammaglobulinemia	<p>Validation</p> <ul style="list-style-type: none"> • 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 <p>Table 3 Subtable 1</p> <p>[14, 15]</p>
<i>PIK3CG</i> (2 patients; 2 families)	AR (LOF)	• Normal CD4, ↓ Treg, ↓ CD8	• Normal but ↓ memory B cells	• Hypogamma	<p>Validation</p> <ul style="list-style-type: none"> • Almost recapitulates the mouse model [12, 13] • Cytopenia/lymphopenia, eosinophilia, lymphadenopathy, splenomegaly, recurrent infections • HLH-like; ↑ inflammatory markers <p>Table 3 Subtable 2</p> <p>[16, 17]</p>
<i>CTNNB1</i> (1 patient)	AR (LOF)	↓ T cells	• Reduced memory B cells; • Impaired CSR, SHM	• Progressive severe hypogamma	<p>Validation</p> <ul style="list-style-type: none"> • ↓ T cell proliferation, activation in vitro • Cellular defects recapitulated in <i>PIK3CG</i> targeted Jurkat T cell line and <i>Plk3eg</i> ko mice <p>Table 3 Subtable 3</p> <p>[18]</p>
<i>TNFSF13</i> (APRIL; 1 patient)	AR (LOF)	• Normal T/NK cells	Normal total B cell counts,	• Hypogamma	<p>Validation</p> <ul style="list-style-type: none"> • detailed functional analysis of <i>CTNNB1</i> variant in EBV B lines, and engineered RAMOS cell lines; • mutant allele reduces the binding of <i>CTNNB1</i> to AID, with impaired nuclear translocation of AID; • defective SHM rescued in mutant Ramos cells by WT <i>CTNNB1</i> <p>Table 3 Subtable 3</p> <p>[19]</p>

Table 1 (continued)

<p><i>SOC1</i> (15 patients; 10 families)</p>	<p>AD (by haploinsufficiency)</p>	<ul style="list-style-type: none"> • ↓ CD4, CD8 T cells 	<ul style="list-style-type: none"> • ↑ IgM+ marginal zone / ↓ sw memory B cells, • ↓ blood plasmablasts 	<ul style="list-style-type: none"> • ↓ IgM, G, A but protective specific Abs; ANA's, autoAbs • ↑ serum BAFF 	<ul style="list-style-type: none"> • 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 • Evan's syndrome • 1 patient developed COVID19/MIS-C • neutropenia, lymphopenia • incomplete penetrance 	<p>Table 4 Subtable 4 [20–22]</p>
		<ul style="list-style-type: none"> • ↑ DN T cells • ↓ Th1, Th17, Tfh cells 	<ul style="list-style-type: none"> • Predom naive B cells • ↓ sw memory, ↑ CD21to B 	<ul style="list-style-type: none"> • ↓ Memory B cells • Impaired B cell diff in vitro to plasma cells 	<p>Validation</p> <ul style="list-style-type: none"> • ↑ pSTAT1, ↑ type I/II IFN signature • Reporter assays confirmed impaired inhibition of mutant SOCS • Jakinib effective in vitro and in vivo. • ALPS-like (↑ sCD25, sFasL, IL10) • Recurrent viral infections, lymphadenopathy, hepatosplenomegaly, autoimmunity (cytopenias, B cell lymphoma (EBV+ HL-like) • Failure to thrive, developmental delay • EBV viremia • DNA hypermethylation • Defective FAS-mediated apoptosis • Recurrent abdominal pain, aseptic fever, systemic inflammation; abscesses, ulceration, infections; mild bleeding diathesis • Autoinflammation activation/↑ IFN gene expression (autoinflammation, immunodeficiency, neutrophil dysfunction) 	<p>Table 4 Subtable 7 [23]</p>
<p><i>CEBPE</i> (3 patients, 1 family)</p>	<p>AR (GOF)</p>	<ul style="list-style-type: none"> • Mild lymphopenia • ↓ naive, ↑ T_{EMRA} cells 	<p>ND</p>	<p>ND</p>	<ul style="list-style-type: none"> • homozygous <i>CEBPE</i> variant affecting DNA binding domain, associated with autoinflammation/immunodeficiency • showed altered chromatin occupancy of mutant <i>CEBPE</i>, and transcriptional changes, in patient cells targeting inflammasome and IFN-related genes 	<p>Table 5 Subtable 2 [24]</p>
<p><i>TBX21</i> (T-bet; 1 patient)</p>	<p>AR (LOF)</p>	<ul style="list-style-type: none"> • Normal %'s total, CD4 and CD8 T cells, naive and memory subsets, low frequencies of NK cells • ↓ CXCR3⁺CCR6⁺ Th1 cells, CXCR3⁺ Th and CXCR3⁺ Treg CD4⁺ T cells • ↑ immature NK • ↓ iNKT, MAIT, Vδ2⁺ γδ T cells 	<ul style="list-style-type: none"> • Normal 	<ul style="list-style-type: none"> • Normal 	<ul style="list-style-type: none"> • MSMD • ↓ IFN-γ and TNF-α production by T cell subsets (γδ T cells, MAIT cells, iNKT cells, NK cells, Vδ2⁺γδ, Vδ1⁺γδ, and CD4⁺ T cells 	<p>Table 6 Subtable 1 [25]</p>
		<p>Validation</p> <ul style="list-style-type: none"> • Biochemical and molecular analysis established the impact of this variant on Tbet function; • Impaired production of IFNγ, TNFα by <i>TBX21</i>-mutant naive CD4⁺ T cells under Th1 polarizing cultured in vitro • Tbet-dependent functions restored in patient cells and cell lines by WT <i>TBX21</i> 				

Table 1 (continued)

	AR (LOF)			MSMD/BCG-osis	Table 6 Subtable 1
<i>IFNG</i> (2 patients [cousins])	<ul style="list-style-type: none"> • Normal frequencies of T and NK cells; • ↑ proportions of naive CD4+ and CD8+ T cells; • ↓ frequency of invariant iNKT 	<ul style="list-style-type: none"> • Normal B cell frequencies; • ↓ memory B cells (↓ IgA+ / IgM+, ↑ IgG+ memory B cells) 	<ul style="list-style-type: none"> • Normal 	<ul style="list-style-type: none"> • No IFN-γ producing cells <p>Validation</p> <ul style="list-style-type: none"> • LOE and LOF allele • Biochemical and molecular analysis established impact of this variant on IFN-γ production from patients' cells • No IFN-γ production by T and NK cells; • Impaired IFN-γ production by patient-derived Herpesvirus <i>saimiri</i>-immortalized T cells restored by introduction of WT <i>IFNG</i> 	[26]
<i>NOS2</i> (1 patient)	<ul style="list-style-type: none"> • ↓ CD4+ T cells; • ↓ NK cells (mostly all immature cells) • normal CD8+ T 	↓ B cells	ND (specific Ab levels normal)	<ul style="list-style-type: none"> • Severe susceptibility to CMV-induced disease; fatal • Pneumocystis pneumonia secondary to CMV • Apparent intact responses to infection with other herpes viruses (EBV, VZV, HSV) <p>Validation:</p> <ul style="list-style-type: none"> • Confirmed functional defect in transfected cells; truncated NOS2 failed to induce nitrous oxide • Recapitulates susceptibility of <i>Mos2</i> deficient mice to murine CMV infection [27] (these mice are also susceptible to numerous other pathogens) 	Table 6 Subtable 3
<i>SNORA31</i> (5 patients, unrelated)	• Normal	• Normal	• Seropositive for IgG against many viruses	<ul style="list-style-type: none"> • Forebrain herpes simplex virus-1 (HSV-1) encephalitis <p>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 <i>SNORA31</i> to HSV1 infection, corrected by exogenous IFN-β</p>	Table 6 Subtable 4
<i>ATG4A</i> (1 patient)	Normal	Normal	Normal	<ul style="list-style-type: none"> • Incomplete penetrance • Mollaret's meningitis (recurrent lymphocytic meningitis) due to HSV2 • History of multiple episodes of meningitis; HSV2+ <p>Validation</p> <ul style="list-style-type: none"> • Impaired HSV2-induced autophagy → increased viral replication and apoptosis of patient fibroblasts 	Table 6 Subtable 4
<i>MAP1LC3B2</i> (1 patient)	Normal	Normal	Normal	<ul style="list-style-type: none"> • These defects were rescued by introduction of WT <i>ATG4</i> or <i>LC3B2</i> into patient fibroblasts 	[30]

Table 1 (continued)

<p>MAPK8 (3 patients, 1 family)</p>	<p>AD (haploinsufficiency)</p>	<p>• Normal total T cells, CD4⁺ and CD8⁺ T subsets, NK cells • ↓ Th17 cells</p>	<p>• Normal total B cells and subsets</p>	<p>• Normal • Chronic mucocutaneous candidiasis (CMC) • 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-dependant TGF β signaling Validation • <i>MAPK8</i> variant LOE in HEK293 T, heterozygous patients' cells (↓ Th17 cells ex vivo, in vitro; ↓ fibroblast responses to IL-17A, IL-17F; ↓ TGFβ signaling) • Defective responses of fibroblasts restored by WT <i>MAPK8</i> • Aicardi-Goutieres syndrome (type 1 IFN-opathy)</p>	<p>Table 6 Subtable 6 [31]</p>
<p>LSM11 (2 siblings, 1 family)</p>	<p>AR (LOF)</p>	<p>Not reported</p>		<p>• Variable (↓) IgM, G, A, E</p>	<p>Table 7 Subtable 1 [32]</p>
<p>RNU7-1 (16 patients, 11 kindreds)</p>	<p>AD</p>	<p>• Normal/decreased T cell numbers, • normal %CD4/CD8 but skewed differentiation</p>	<p>• Normal/B-lymphopenia</p>	<p>• Neonatal onset: pancytopenia, fever, rash, hepatosplenomegaly, systemic inflammation, myelofibrosis/proliferation, HLH, multisystemic inflammatory disease. • ↑ serum levels of IL1, IL18, IFN-γ, ferritin, sCD25, CRP etc. • Recurrent GIT/RT infection; • Neurodevelopmental delay, FTT • Mutation affects actin function; • Treated with Anakinra/ IFN-γ mAb ↓NK function (cytox),</p>	<p>Table 7 Subtable 1 [33–39]</p>
<p>STAT2 (<i>GOF</i>, 3 patients; all deceased; 2 additional deceased sibs but not genotyped; 2 unrelated families)</p>	<p>AR (<i>GOF</i>)</p>	<p>• Low frequency of NK, ↑ frequency of T cells (esp naive), normal NK degranulation</p>	<p>• Total B cell frequencies within age-matched controls' ranges • slight ↑ transitional and naive B cells %'s</p>	<p>• Low/normal</p>	<p>Table 7 Subtable 1 [40, 41]</p>
<p>STAT2 (<i>GOF</i>, 3 patients; all deceased; 2 additional deceased sibs but not genotyped; 2 unrelated families)</p>	<p>AR (<i>GOF</i>)</p>	<p>• Low frequency of NK, ↑ frequency of T cells (esp naive), normal NK degranulation</p>	<p>• Total B cell frequencies within age-matched controls' ranges • slight ↑ transitional and naive B cells %'s</p>	<p>• Severe fatal early-onset autoinflammation (skin ulceration, fever, seizures, intracranial calcification, multiorgan dysfunction, abnormal neurodevelopment; phenocopy of USPI8 deficiency) • ↑ serum IFN-α, IL6, TNFα • IFN-opathy gene signature (impaired regulation of late cellular responses to type 1 IFN), Validation • Study of the mutant <i>STAT2</i> alleles in <i>STAT2</i> deficient human cell line, and patient's immortalized fibroblasts</p>	<p>Table 7 Subtable 1 [40, 41]</p>

Table 1 (continued)

				<ul style="list-style-type: none"> • Patient cells hyper-sensitive to IFN-α \rightarrow 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 1 IFN responses • Autoinflamm disorder: regular/prolonged fevers, lymphadenopathy, spleno/hepatomegaly, ulcers, arthralgia, GI features, <ul style="list-style-type: none"> • \uparrow inflamm markers, \uparrow pro-inflamm cytokines/gene signature; • Responsive to Tocilizumab (not IL1/TNF blockade) 	Table 7 Subtable 2	[42, 43]
RIPK1 (12 patients; 5 families, 2 papers)	AD	<ul style="list-style-type: none"> • Normal T and NK cell numbers • Normal B cells • Low/normal CD4⁺ T cells • Normal/hi CD8⁺ T cells • \uparrow DN T cells 	ND			
NCKAP1 (9 patients; 7 families, 3 papers)	AR (LOF)	<ul style="list-style-type: none"> • Normal T cell numbers • \uparrow T_{CMV}-exhausted cells; • Possibly immature NK cells but intact function 	<ul style="list-style-type: none"> • Normal B cells and naïve/memory subsets • Normal/ \uparrow Ig levels • autoAbs • \uparrow CD21^{lo} cells 		Table 7 Subtable 3	[44–46]
UBAI (25 patients)	XL (somatic LOF mutations)	<ul style="list-style-type: none"> • \downarrow Peripheral lymphocyte counts • Loss of immature B cells, nonclassical and intermediate monocyte populations 			Table 7	[47]

Table 1 (continued)

Novel phenocopies of inborn errors of immunity	Disease	Mechanisms of disease pathogenesis	Associated/clinical features	Table	Refs
Severe COVID-19	<ul style="list-style-type: none"> Defective ubiquitylation of patients' mutant monocytes CRISPR-Cas9 <i>Uba1</i>-deficient zebrafish model recapitulates the phenotype of systemic inflammation 	<ul style="list-style-type: none"> High levels of neutralizing autoAbs against type 1 IFNs (primarily IFNα, IFNω) 	<ul style="list-style-type: none"> 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 OTFCS2 (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)
- *Fnuip1* 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

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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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References


- Notarangelo LD, Bacchetta R, Casanova JL, Su HC. Human inborn errors of immunity: an expanding universe. *Sci Immunol*. 2020;5(49):eabb1662. <https://doi.org/10.1126/sciimmunol.abb1662>.
- Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *J Clin Immunol*. 2020;40(1):66–81. <https://doi.org/10.1007/s10875-020-00758-x>.
- Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human inborn errors of immunity: 2019 update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. 2020;40(1):24–64. <https://doi.org/10.1007/s10875-019-00737-x>.
- Meyts I, Bosch B, Bolze A, Boisson B, Itan Y, Belkadi A, et al. Exome and genome sequencing for inborn errors of immunity. *J Allergy Clin Immunol*. 2016;138(4):957–69. <https://doi.org/10.1016/j.jaci.2016.08.003>.
- Yamazaki Y, Urrutia R, Franco LM, Giliani S, Zhang K, Alazami AM, et al. PAX1 is essential for development and function of the human thymus. *Sci Immunol*. 2020;5(44):eaax1036. <https://doi.org/10.1126/sciimmunol.aax1036>.
- Paganini I, Sestini R, Capone GL, Putignano AL, Contini E, Giotti I, et al. A novel PAX1 null homozygous mutation in autosomal recessive otofaciocervical syndrome associated with severe combined immunodeficiency. *Clin Genet*. 2017;92(6):664–8. <https://doi.org/10.1111/cge.13085>.
- Lev A, Lee YN, Sun G, Hallumi E, Simon AJ, Zrihen KS, et al. Inherited SLP76 deficiency in humans causes severe combined immunodeficiency, neutrophil and platelet defects. *J Exp Med*. 2021;218(3):e20201062. <https://doi.org/10.1084/jem.20201062>.
- Mace EM, Paust S, Conte MI, Baxley RM, Schmit MM, Patil SL, et al. Human NK cell deficiency as a result of biallelic mutations in MCM10. *J Clin Invest*. 2020;130:5272–86. <https://doi.org/10.1172/JCI134966>.
- Beziat V, Tavernier SJ, Chen YH, Ma CS, Materna M, Laurence A, et al. Dominant-negative mutations in human IL6ST underlie hyper-IgE syndrome. *J Exp Med*. 2020;217(6):e20191804. <https://doi.org/10.1084/jem.20191804>.
- Monies D, Abouelhoda M, Assoum M, Moghrabi N, Rafiullah R, Almontashiri N, et al. Lessons learned from large-scale, first-tier clinical exome sequencing in a highly consanguineous population. *Am J Hum Genet*. 2019;104(6):1182–201. <https://doi.org/10.1016/j.ajhg.2019.04.011>.
- Chen YH, Grigelioniene G, Newton PT, Gullander J, Elfving M, Hammarsjo A, et al. Absence of GP130 cytokine receptor signaling causes extended Stuve-Wiedemann syndrome. *J Exp Med*. 2020;217(3):e20191306. <https://doi.org/10.1084/jem.20191306>.
- Park H, Staehling K, Tsang M, Appleby MW, Brunkow ME, Margineantu D, et al. Disruption of FcγR1 reveals a metabolic checkpoint controlling B lymphocyte development. *Immunity*. 2012;36(5):769–81. <https://doi.org/10.1016/j.immuni.2012.02.019>.
- Siggs OM, Stockenhuber A, Deobagkar-Lele M, Bull KR, Crockford TL, Kingston BL, et al. Mutation of FcγR1 is associated with B-cell deficiency, cardiomyopathy, and elevated AMPK activity. *Proc Natl Acad Sci U S A*. 2016;113(26):E3706–15. <https://doi.org/10.1073/pnas.1607592113>.
- Niehues T, Ozgur TT, Bickes M, Waldmann R, Schoning J, Brasen J, et al. Mutations of the gene FNIP1 associated with a syndromic autosomal recessive immunodeficiency with cardiomyopathy and pre-excitation syndrome. *Eur J Immunol*. 2020;50(7):1078–80. <https://doi.org/10.1002/eji.201948504>.
- Saettini F, Poli C, Vengoechea J, Bonanomi S, Orellana JC, Fazio G, et al. Absent B cells, agammaglobulinemia, and hypertrophic cardiomyopathy in folliculin interacting protein 1 deficiency. *Blood*. 2021;137:493–9. <https://doi.org/10.1182/blood.202006441>.
- Takeda AJ, Maher TJ, Zhang Y, Lanahan SM, Bucklin ML, Compton SR, et al. Human PI3Kγ deficiency and its microbiota-dependent mouse model reveal immunodeficiency and tissue immunopathology. *Nat Commun*. 2019;10(1):4364. <https://doi.org/10.1038/s41467-019-12311-5>.
- Thian M, Hoeger B, Kamnev A, Poyer F, Kostel Bal S, Caldera M, et al. Germline biallelic PIK3CG mutations in a multifaceted

- immunodeficiency with immune dysregulation. *Haematologica*. 2020;105:e488. <https://doi.org/10.3324/haematol.2019.231399>.
18. Kuhny M, Forbes LR, Cakan E, Vega-Loza A, Kostiuik V, Dinesh RK, et al. Disease-associated CTNBL1 mutation impairs somatic hypermutation by decreasing nuclear AID. *J Clin Invest*. 2020;130(8):4411–4422. <https://doi.org/10.1172/JCI131297>.
 19. Yeh TW, Okano T, Naruto T, Yamashita M, Okamura M, Tanita K, et al. APRIL-dependent life-long plasmacyte maintenance and immunoglobulin production in humans. *J Allergy Clin Immunol*. 2020;146:1109–1120.e4. <https://doi.org/10.1016/j.jaci.2020.03.025>.
 20. Lee PY, Platt CD, Weeks S, Grace RF, Maher G, Gauthier K, et al. Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of SOCS1. *J Allergy Clin Immunol*. 2020;146(5):1194–1200.e1. <https://doi.org/10.1016/j.jaci.2020.07.033>.
 21. Thaventhiran JED, Lango Allen H, Burren OS, Rae W, Greene D, Staples E, et al. Whole-genome sequencing of a sporadic primary immunodeficiency cohort. *Nature*. 2020;583(7814):90–5. <https://doi.org/10.1038/s41586-020-2265-1>.
 22. Hadjadj J, Castro CN, Tusseau M, Stolzenberg MC, Mazerolles F, Aladjidi N, et al. Early-onset autoimmunity associated with SOCS1 haploinsufficiency. *Nat Commun*. 2020;11(1):5341. <https://doi.org/10.1038/s41467-020-18925-4>.
 23. Stremenova Spegarova J, Lawless D, Mohamad SMB, Engelhardt KR, Doody G, Shrimpton J, et al. Germline TET2 loss of function causes childhood immunodeficiency and lymphoma. *Blood*. 2020;136(9):1055–66. <https://doi.org/10.1182/blood.2020005844>.
 24. Goos H, Fogarty CL, Sahu B, Plagnol V, Rajamaki K, Nurmi K, et al. Gain-of-function CEBPE mutation causes noncanonical autoinflammatory inflammasomopathy. *J Allergy Clin Immunol*. 2019;144(5):1364–76. <https://doi.org/10.1016/j.jaci.2019.06.003>.
 25. Yang R, Mele F, Worley L, Langlais D, Rosain J, Benhsaien I, et al. Human T-bet governs innate and innate-like adaptive IFN- γ immunity against mycobacteria. *Cell*. 2020;183(7):1826–1847.e31. <https://doi.org/10.1016/j.cell.2020.10.046>.
 26. Kerner G, Rosain J, Guerin A, AlKhabaz A, Oleaga-Quintas C, Rapaport F, et al. Inherited human IFN γ deficiency underlies mycobacterial disease. *J Clin Invest*. 2020;130(6):3158–71. <https://doi.org/10.1172/JCI135460>.
 27. Noda S, Tanaka K, Sawamura S, Sasaki M, Matsumoto T, Mikami K, et al. Role of nitric oxide synthase type 2 in acute infection with murine cytomegalovirus. *J Immunol*. 2001;166(5):3533–41. <https://doi.org/10.4049/jimmunol.166.5.3533>.
 28. Drutman SB, Mansouri D, Mahdavi SA, Neehus AL, Hum D, Bryk R, et al. Fatal Cytomegalovirus infection in an adult with inherited NOS2 deficiency. *N Engl J Med*. 2020;382(5):437–45. <https://doi.org/10.1056/NEJMoa1910640>.
 29. Lafaille FG, Harschnitz O, Lee YS, Zhang P, Hasek ML, Kerner G, et al. Human SNORA31 variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis. *Nat Med*. 2019;25(12):1873–84. <https://doi.org/10.1038/s41591-019-0672-3>.
 30. Hait AS, Olganier D, Sancho-Shimizu V, Skipper KA, Helleberg M, Larsen SM, et al. Defects in LC3B2 and ATG4A underlie HSV2 meningitis and reveal a critical role for autophagy in antiviral defense in humans. *Sci Immunol*. 2020;5(54):eabc2691. <https://doi.org/10.1126/sciimmunol.abc2691>.
 31. Li J, Ritelli M, Ma CS, Rao G, Habib T, Corvilain E, et al. Chronic mucocutaneous candidiasis and connective tissue disorder in humans with impaired JNK1-dependent responses to IL-17A/F and TGF- β . *Sci Immunol*. 2019;4(41):eabc2691. <https://doi.org/10.1126/sciimmunol.aax7965>.
 32. Ugenti C, Lepelley A, Depp M, Badrock AP, Rodero MP, El-Daher MT, et al. cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing. *Nat Genet*. 2020;52(12):1364–72. <https://doi.org/10.1038/s41588-020-00737-3>.
 33. Verboon JM, Mahmut D, Kim AR, Nakamura M, Abdulhay NJ, Nandakumar SK, et al. Infantile myelofibrosis and myeloproliferation with CDC42 dysfunction. *J Clin Immunol*. 2020;40:554–66. <https://doi.org/10.1007/s10875-020-00778-7>.
 34. Lam MT, Coppola S, Krumbach OHF, Prencipe G, Insalaco A, Cifaldi C, et al. A novel disorder involving dyshematopoiesis, inflammation, and HLH due to aberrant CDC42 function. *J Exp Med*. 2019;216(12):2778–99. <https://doi.org/10.1084/jem.20190147>.
 35. Gernez Y, de Jesus AA, Alsaleem H, Macaubas C, Roy A, Lovell D, et al. Severe autoinflammation in 4 patients with C-terminal variants in cell division control protein 42 homolog (CDC42) successfully treated with IL-1 β inhibition. *J Allergy Clin Immunol*. 2019;144(4):1122–5 e6. <https://doi.org/10.1016/j.jaci.2019.06.017>.
 36. Bucciol G, Pillay B, Casas-Martin J, Delafontaine S, Proesmans M, Lorent N, et al. Systemic inflammation and myelofibrosis in a patient with Takenouchi-Kosaki syndrome due to CDC42 Tyr64Cys mutation. *J Clin Immunol*. 2020;40:567–70. <https://doi.org/10.1007/s10875-020-00742-5>.
 37. Bekhouche B, Tourville A, Ravichandran Y, Tacine R, Abrami L, Dussiot M, et al. A toxic palmitoylation of Cdc42 enhances NF- κ B signaling and drives a severe autoinflammatory syndrome. *J Allergy Clin Immunol*. 2020;146(5):1201–1204.e8. <https://doi.org/10.1016/j.jaci.2020.03.020>.
 38. He T, Huang Y, Ling J, Yang J. A new patient with NOCARH syndrome due to CDC42 defect. *J Clin Immunol*. 2020;40(4):571–5. <https://doi.org/10.1007/s10875-020-00786-7>.
 39. Szczawinska-Poplonyk A, Ploski R, Bernatowska E, Pac M. A novel CDC42 mutation in an 11-year old child manifesting as syndromic immunodeficiency, autoinflammation, hemophagocytic lymphohistiocytosis, and malignancy: a case report. *Front Immunol*. 2020;11:318. <https://doi.org/10.3389/fimmu.2020.00318>.
 40. Gruber C, Martin-Fernandez M, Ailal F, Qiu X, Taft J, Altman J, et al. Homozygous STAT2 gain-of-function mutation by loss of USP18 activity in a patient with type I interferonopathy. *J Exp Med*. 2020;217(5):e20192319. <https://doi.org/10.1084/jem.20192319>.
 41. Duncan CJA, Thompson BJ, Chen R, Rice GI, Gothe F, Young DF, et al. Severe type I interferonopathy and unrestrained interferon signaling due to a homozygous germline mutation in STAT2. *Sci Immunol*. 2019;4(42):eaav7501. <https://doi.org/10.1126/sciimmunol.aav7501>.
 42. Tao P, Sun J, Wu Z, Wang S, Wang J, Li W, et al. A dominant autoinflammatory disease caused by non-cleavable variants of RIPK1. *Nature*. 2020;577(7788):109–14. <https://doi.org/10.1038/s41586-019-1830-y>.
 43. Lalaoui N, Boyden SE, Oda H, Wood GM, Stone DL, Chau D, et al. Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. *Nature*. 2020;577(7788):103–8. <https://doi.org/10.1038/s41586-019-1828-5>.
 44. Cook SA, Comrie WA, Poli MC, Similuk M, Oler AJ, Faruqi AJ, et al. HEM1 deficiency disrupts mTORC2 and F-actin control in inherited immunodysregulatory disease. *Science*. 2020;369(6500):202–7. <https://doi.org/10.1126/science.aay5663>.
 45. Salzer E, Zoghi S, Kiss MG, Kage F, Rashkova C, Stahnke S, et al. The cytoskeletal regulator HEM1 governs B cell development and prevents autoimmunity. *Sci Immunol*. 2020;5(49):eabc3979. <https://doi.org/10.1126/sciimmunol.abc3979>.
 46. Castro CN, Rosenzweig M, Carapito R, Shahrooei M, Konantz M, Khan A, et al. NCKAP1L defects lead to a novel syndrome combining immunodeficiency, lymphoproliferation, and hyperinflammation. *J Exp Med*. 2020;217(12):e20192275. <https://doi.org/10.1084/jem.20192275>.

47. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N Engl J Med*. 2020;383:2628–38. <https://doi.org/10.1056/NEJMoa2026834>.
48. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;370(6515):eabd4585. <https://doi.org/10.1126/science.abd4585>.
49. Pohl E, Aykut A, Beleggia F, Karaca E, Durmaz B, Keupp K, et al. A hypofunctional PAX1 mutation causes autosomally recessively inherited otofaciocervical syndrome. *Hum Genet*. 2013;132(11):1311–20. <https://doi.org/10.1007/s00439-013-1337-9>.
50. Spencer S, Kostel Bal S, Egnér W, Lango Allen H, Raza SI, Ma CA, et al. Loss of the interleukin-6 receptor causes immunodeficiency, atopy, and abnormal inflammatory responses. *J Exp Med*. 2019;216(9):1986–98. <https://doi.org/10.1084/jem.20190344>.
51. Gombart AF, Koeffler HP. Neutrophil specific granule deficiency and mutations in the gene encoding transcription factor C/EBP(epsilon). *Curr Opin Hematol*. 2002;9(1):36–42. <https://doi.org/10.1097/00062752-200201000-00007>.
52. Su HC, Orange JS. The growing spectrum of human diseases caused by inherited CDC42 mutations. *J Clin Immunol*. 2020;40(4):551–3. <https://doi.org/10.1007/s10875-020-00785-8>.
53. Hambleton S, Goodbourn S, Young DF, Dickinson P, Mohamad SM, Valappil M, et al. STAT2 deficiency and susceptibility to viral illness in humans. *Proc Natl Acad Sci U S A*. 2013;110(8):3053–8. <https://doi.org/10.1073/pnas.1220098110>.
54. Moens L, Van Eyck L, Jochmans D, Mitera T, Frans G, Bossuyt X, et al. A novel kindred with inherited STAT2 deficiency and severe viral illness. *J Allergy Clin Immunol*. 2017;139(6):1995–7 e9. <https://doi.org/10.1016/j.jaci.2016.10.033>.
55. Cuchet-Lourenco D, Eletto D, Wu C, Plagnol V, Papapietro O, Curtis J, et al. Biallelic RIPK1 mutations in humans cause severe immunodeficiency, arthritis, and intestinal inflammation. *Science*. 2018;361(6404):810–3. <https://doi.org/10.1126/science.aar2641>.
56. Li Y, Fuhrer M, Bahrami E, Socha P, Klaudel-Dreszler M, Bouzidi A, et al. Human RIPK1 deficiency causes combined immunodeficiency and inflammatory bowel diseases. *Proc Natl Acad Sci U S A*. 2019;116(3):970–5. <https://doi.org/10.1073/pnas.1813582116>.
57. Casanova JL, Conley ME, Seligman SJ, Abel L, Notarangelo LD. Guidelines for genetic studies in single patients: lessons from primary immunodeficiencies. *J Exp Med*. 2014;211(11):2137–49. <https://doi.org/10.1084/jem.20140520>.
58. Bustamante J. Mendelian susceptibility to mycobacterial disease: recent discoveries. *Hum Genet*. 2020;139(6–7):993–1000. <https://doi.org/10.1007/s00439-020-02120-y>.
59. Moens L, Meyts I. Recent human genetic errors of innate immunity leading to increased susceptibility to infection. *Curr Opin Immunol*. 2020;62:79–90. <https://doi.org/10.1016/j.coi.2019.12.002>.
60. Zhang SY. Herpes simplex virus encephalitis of childhood: inborn errors of central nervous system cell-intrinsic immunity. *Hum Genet*. 2020;139(6–7):911–8. <https://doi.org/10.1007/s00439-020-02127-5>.
61. Casanova JL, Holland SM, Notarangelo LD. Inborn errors of human JAKs and STATs. *Immunity*. 2012;36(4):515–28. <https://doi.org/10.1016/j.immuni.2012.03.016>.
62. Shahin T, Aschenbrenner D, Cagdas D, Bal SK, Conde CD, Gamcarz W, et al. Selective loss of function variants in IL6ST cause hyper-IgE syndrome with distinct impairments of T-cell phenotype and function. *Haematologica*. 2019;104(3):609–21. <https://doi.org/10.3324/haematol.2018.194233>.
63. Nahum A, Sharfe N, Broides A, Dadi H, Naghdi Z, Mandola AB, et al. Defining the biological responses of IL-6 by the study of a novel IL-6 receptor chain immunodeficiency. *J Allergy Clin Immunol*. 2020;145(3):1011–5 e6. <https://doi.org/10.1016/j.jaci.2019.11.015>.
64. Puel A, Picard C, Lorrot M, Pons C, Chrabieh M, Lorenzo L, et al. Recurrent staphylococcal cellulitis and subcutaneous abscesses in a child with autoantibodies against IL-6. *J Immunol*. 2008;180(1):647–54. <https://doi.org/10.4049/jimmunol.180.1.647>.
65. Martínez-Barricarte R, Markle JG, Ma CS, Deenick EK, Ramirez-Alejo N, Mele F, et al. Human IFN-gamma immunity to mycobacteria is governed by both IL-12 and IL-23. *Sci Immunol*. 2018;3(30):eaau6759. <https://doi.org/10.1126/sciimmunol.aau6759>.
66. Kotlarz D, Zietara N, Milner JD, Klein C. Human IL-21 and IL-21R deficiencies: two novel entities of primary immunodeficiency. *Curr Opin Pediatr*. 2014;26(6):704–12. <https://doi.org/10.1097/MOP.000000000000160>.
67. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020;370(6515):eabd4570. <https://doi.org/10.1126/science.abd4570>.
68. Zhang Q. Human genetics of life-threatening influenza pneumonitis. *Hum Genet*. 2020;139(6–7):941–8. <https://doi.org/10.1007/s00439-019-02108-3>.
69. Ku CL, Chi CY, von Bernuth H, Doffinger R. Autoantibodies against cytokines: phenocopies of primary immunodeficiencies? *Hum Genet*. 2020;139(6–7):783–94. <https://doi.org/10.1007/s00439-020-02180-0>.
70. Levy R, Bastard P, Lanternier F, Lecuit M, Zhang SY, Casanova JL. IFN-alpha2a therapy in two patients with inborn errors of TLR3 and IRF3 infected with SARS-CoV-2. *J Clin Immunol*. 2021;41:26–7. <https://doi.org/10.1007/s10875-020-00933-0>.

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