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Common Variable Immunodeficiency: More Pathways than Roads to Rome

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Abstract

Fifty years have elapsed since the term common variable immunodeficiency (CVID) was introduced to accommodate the many and varied antibody deficiencies being identified in patients with suspected inborn errors of immunity (IEIs). Since then, how the term is understood and applied for diagnosis and management has undergone many revisions, though controversy persists on how exactly to define and classify CVID. Many monogenic disorders have been added under its aegis, while investigations into polygenic, epigenetic, and somatic contributions to CVID susceptibility have gained momentum. Expansion of the overall IEI landscape has increasingly revealed genotypic and phenotypic overlap between CVID and various other immunological conditions, while increasingly routine genotyping of CVID patients continues to identify an incredible diversity of pathophysiological mechanisms affecting even single genes. Though many questions remain to be answered, the lessons we have already learned from CVID biology have greatly informed our understanding of adaptive, but also innate, immunity.

1. INTRODUCTION

In 1971, the term variable immunodeficiency was introduced by a World Health Organization committee to accommodate "the majority of patients with immunodeficiency" whose "extraordinary variability of immunological findings" could not be "unequivocally classified" on the basis of then-extant criteria (1, p. 938). These were distinguished from the much smaller number of then-known Mendelian immunodeficiencies with the hope that "careful analysis of such patients [would] result in delineation of several homogeneous syndromes based on established hereditary mechanisms or other etiological factors" (1, p. 938). Fifty years later, common variable immunodeficiency (CVID) still "presents a major difficulty in classification," associated with an expanded but still heterogeneous mix of conditions that "presumably includes many [distinct] syndromes because of lack of information on definite patterns and causes" (1, p. 938).

In this review, we discuss the evolution of the understanding of CVID (or, perhaps more accurately, CVIDs) in the genomic era, framing emerging genetic landscapes and pathophysiologies in the context of evolving attempts at definition and classification. As for many phenotypes established in the pregenomic era, the increasing elucidation of monogenic etiologies in CVID patients has engendered controversy—are these monogenic CVIDs or monogenic conditions misdiagnosed as CVID? The distinction is not merely a semantic one but affects how we conceptualize and communicate about CVID going forward. CVID is often considered a diagnosis of clinical exclusion, but we cannot claim to entirely rule out any monogenic etiology using current molecular diagnostic tools. Of particular concern is the risk that the CVID label may confer a false sense of security about diagnosis, potentially blinding clinicians to additional management needs associated with underlying genetic conditions.

In this review, we frame CVID as a clinical diagnosis encompassing a heterogeneous group of conditions, with some arising from robustly penetrant monogenic lesions but the majority involving poorly elucidated oligogenic and polygenic interactions. We focus our attention on the former but also discuss efforts to better understand the latter. The expanding delineation of CVID-associated genetic loci has revealed a broader spectrum of pathophysiologies than previously imagined (**Figure 1**; **Table 1**), but our discussion primarily addresses the recurrent themes and pathways that CVID genetics has shown are required for generating a mature antibody repertoire. For clinical details, see the excellent recent review by Janssen et al. (2).

2. EVOLUTION OF DEFINITIONS AND CLASSIFICATION CRITERIA

The development of diagnostic criteria for CVID has been valuable for helping clinicians navigate its heterogeneity for clinical decision-making. In 1971, variable immunodeficiency encompassed all primary immunodeficiencies not diagnosed as X-linked agammaglobulinemia, selective immunoglobulin A deficiency (sIgAD), X-linked hyper-IgM syndrome (X-HIGM), ataxia telangiectasia, Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID), or a few other clinically distinctive syndromes. While some of these conditions such as sIgAD also remain heterogeneous clinical and molecular entities, the ability to perform upfront molecular diagnosis for suspected monogenic etiologies has expanded their clinical spectrum, rendering boundaries with other inborn errors of immunity (IEIs) less discrete—and in some cases, increasing their overlap with CVID-like phenotypes.

Historically, some groups have focused on evolving the classification of CVID via B cell functional differences or immunophenotypic delineation by flow cytometry, while others emphasized the derivation of clinical criteria from large patient cohorts. With emerging recognition that divergent pathophysiologies may converge upon similar clinical and immunological phenotypes,

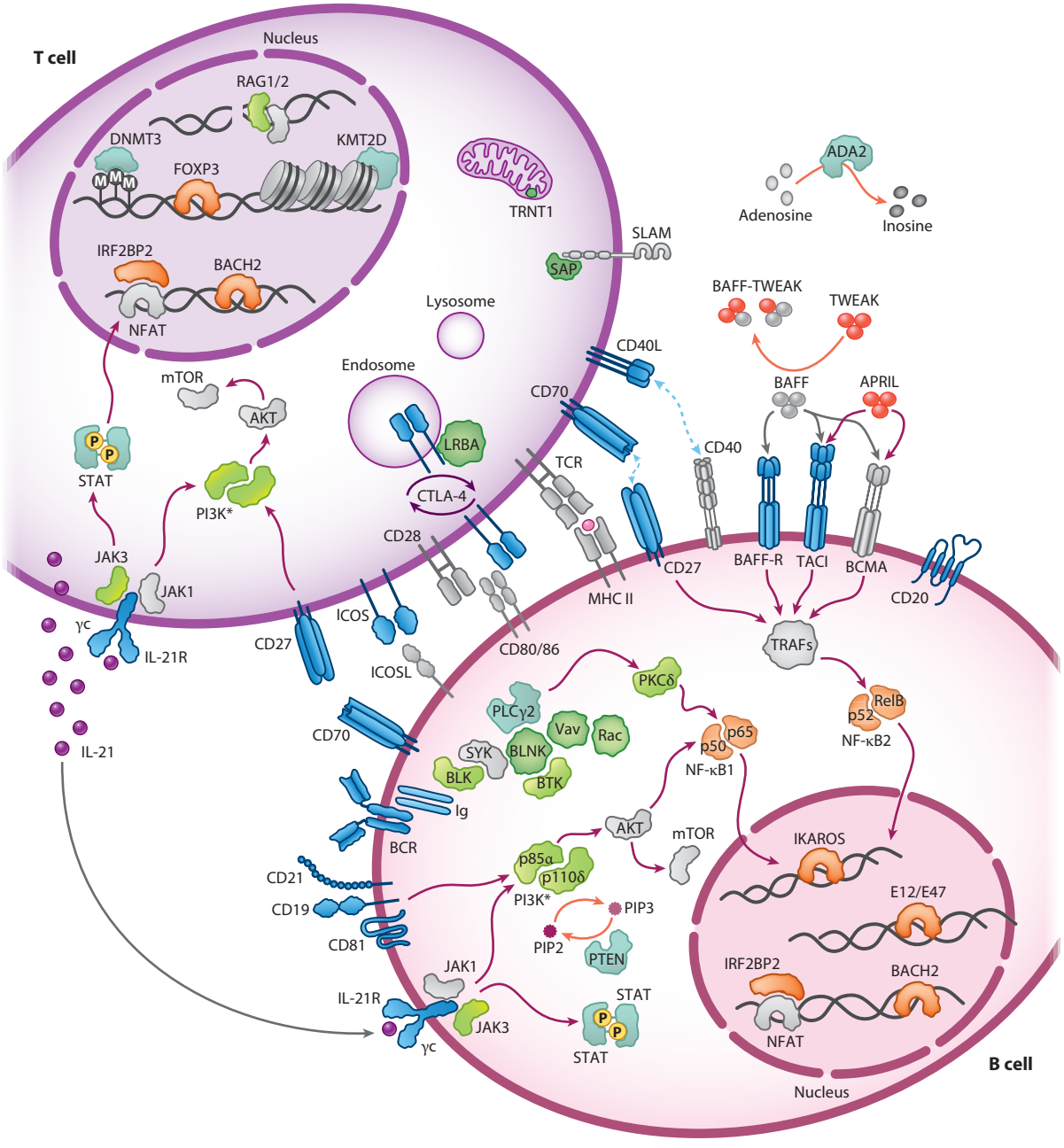

Figure 1

Simplified representation of genes associated with monogenic common variable immunodeficiencies (CVIDs). Subcellular localization and molecular pathways of proteins encoded by genes found mutated in CVID patients are shown. Asterisk indicates that PI3K proteins include p85α (encoded by *PIK3R1*), p110δ (encoded by *PIK3CD*), and p110γ (encoded by *PIK3CG*). E12 and E47 transcription factors are encoded by *TCF3*. Not all genes reviewed in this article are depicted in the figure. Solid purple arrows represent signal transduction interactions, solid red arrows represent molecular state changes, solid gray arrows represent ligand-binding interactions, and blue dashed arrows represent binding interactions between cell surface molecules. Orange bodies represent proteins with roles in transcriptional regulation. Other color distinctions do not correspond to specific representations, but are intended for visual contrast.

Table 1 Monogenic causes of CVID reported in original publications, organized by IUIS classification (159)

IUIS classification	Cause	Gene(s)
Table 1	Immunodeficiencies affecting cellular and humoral immunity	*CD3G*, *CD40LG*, *DCLRE1C*, *ICOS*, *IL21*, *IL21R*[a], *IL2RG*, *JAK3*, *LCK*, *RAG1*, *RAG2*, *RFXANK*, *SASH3*
Table 2	Combined immunodeficiencies with associated or syndromic features	*CARD11* [DN], *DNMT3B*, *KDM6A*, *KMT2A*, *KMT2D*, *PMS2*[a], *RNF31* (HOIP), *RNU4ATAC*, *TTC7A*, *ZBTB24*
Table 3	Predominantly antibody deficiencies	*ARHGEF1*[a], *ATP6AP1*[a], *BTK*, *CD19*, *CD81*, *CR2* (CD21), *CTNNBL1*, *FNIP1*[a], *IKZF1*, *IRF2BP2*, *MOGS*[a], *MS4A1* (CD20), *NFKB1*, *NFKB2*, *PIK3CD*, *PIK3CG*, *PIK3R1*, *PTEN*, *RAC2*, *SEC61A1*[a], *SH3KBP1*[a], *TCF3*, *TNFRSF13B* (TACI), *TNFRSF13C* (BAFFR), *TNFSF12* (TWEAK), *TNFSF13* (APRIL), *TRNT1*
Table 4	Diseases of immune dysregulation	*AIRE*, *BACH2*, *CD27*, *CD70*, *CTLA4*, *DEF6*[a], *FAS*, *FOXP3*, *LRBA*, *MAGT1*, *PRKCD*, *SH2D1A* (*SAP*), *SOCS1*, *STAT3* [GOF], *STXBP2*, *UNC13D*
Table 5	Congenital defects of phagocyte number or function	*SBDS*
Table 6	Defects in intrinsic and innate immunity	*CXCR4*, *STAT1* [GOF]
Table 7	Autoinflammatory disorders	*ADA2*, *PLCG2*, *PSTPIP1*, *SYK* [GOF][a], *TNFAIP3* (A20)
Table 9	Bone marrow failure	*SAMD9*[a]
Table 10	Phenocopies of inborn errors of immunity	*NRAS*
NA	Other primary adaptive immune defects not found in IUIS classification tables	*BLK*, *PTPN2*, *VAV1*

[a]Genes retrospectively linked to CVID phenotypes (see **Supplemental Table 3** for details).
Abbreviations: CVID, common variable immunodeficiency; DN, dominant negative; GOF, gain of function; IUIS, International Union of Immunological Societies; NA, not applicable.

Supplemental Material >

CVID criteria have been blended and new strategies and biomarkers have been incorporated; their goals of use have been reframed as well. Taken together, these studies (**Figure 2**; **Supplemental Table 1**) suggest distinct but overlapping mechanisms underlying CVID subpopulations but also highlight ongoing challenges of predicting divergent natural histories.

The advent of next-generation sequencing (NGS) and other omics-based technologies has enabled the high-throughput examination of additional biomarkers for stratifying CVID patients into shared pathophysiologies and outcomes that may be incorporated into future classifications (3). These include studies interrogating differences in gene expression, DNA methylation, B cell receptor (BCR) and T cell receptor (TCR) repertoires, gut microbiome diversity, proteomics, and metabolomics, as well as emerging efforts to integrate genotyping data with descriptive parameters [**Supplemental Table 2**; see also the excellent recent review by Ho & Cunningham-Rundles (4)].

Despite extensive ongoing efforts, we remain far from universal consensus on how to define and apply the term CVID. Indeed, some studies suggest that such a one-size-fits-all approach may not be realistic (5). Though more and more studies are reporting unbiased genotyping-first approaches to CVID, this continues to be limited in routine clinical practice and faces the same challenges of variant triage, classification, and validation as other IEIs (6). Going forward, more rigorous phenotype-driven stratification may enhance our ability to capture distinct genetic contributions, while more routine and responsible interpretation of patient genotyping data in the context of increasingly multidimensional clinical and immunophenotypic data may help further unravel the pathophysiological complexities of CVID.

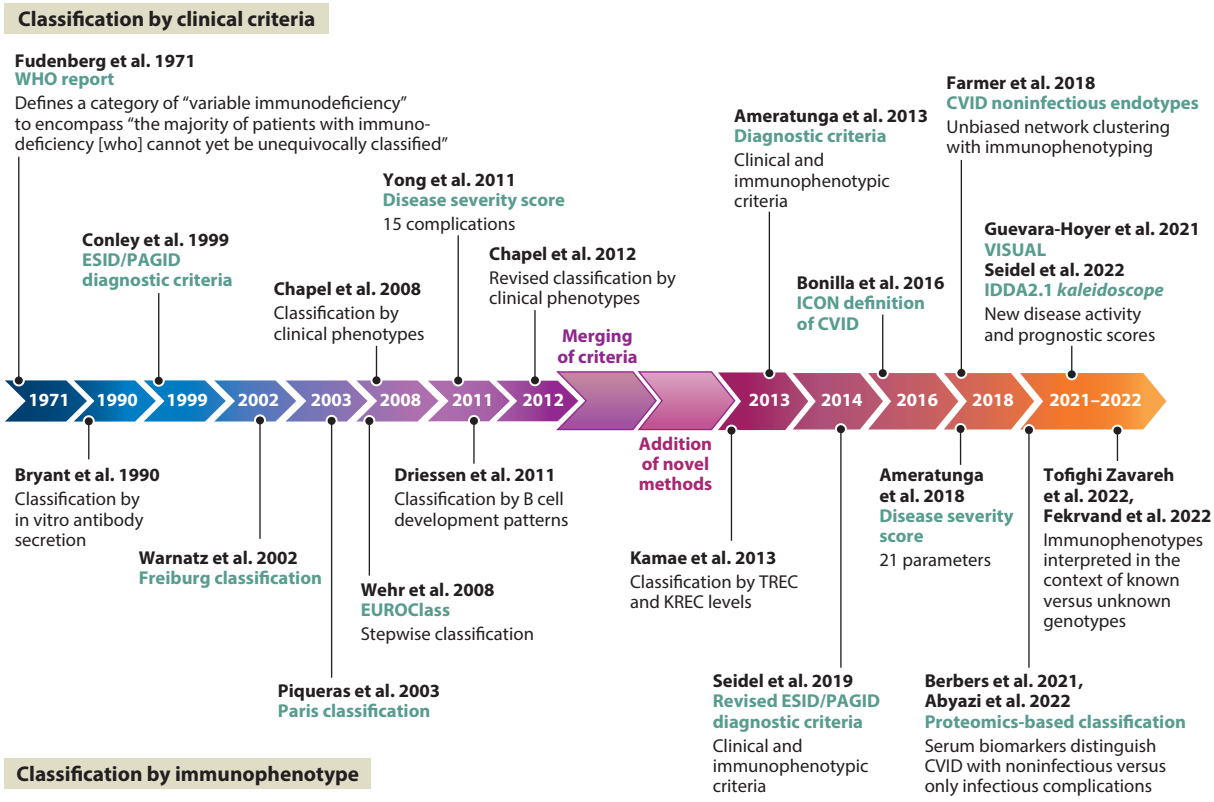

Figure 2

Evolution of CVID classification criteria and definitions. The timeline shows representative changes over time in the proposed criteria for classifying, defining, or diagnosing CVID. Some examples of different approaches are provided (not a comprehensive list). Note that time differences between dates of publications are not drawn to scale. Full details can be found in **Supplemental Tables 1 and 2** and References 1, 5, 65, 148, and 160–177. Abbreviations: CVID, common variable immunodeficiency; ESID/PAGID, European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency; ICON, international consensus; WHO, World Health Organization.

3. CVIDs WITH MONOGENIC ETIOLOGIES

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As for other complex conditions such as systemic lupus erythematosus (SLE) or inflammatory bowel disease, the identification of rare monogenic etiologies has highlighted pathophysiologies and treatments potentially shared with more prevalent polygenic disease. More than 60 monogenic CVIDs have been identified over the last 20 years (**Figure 3**; **Supplemental Figure 1**), with an additional 11 genes noted by subsequent publications to cause a CVID phenotype without explicit CVID diagnoses in the original reports (**Supplemental Table 3**). For each gene, **Figure 4** shows the number of unaffected carriers and patients diagnosed with CVID versus other clinical phenotypes. Our discussion centers around the contributions to CVID made by pathogenic variation in these genes, organized by shared clinical (**Table 1**) and mechanistic (**Supplemental Figures 3 and 4**) features. We recognize the preference for the more precise term pathogenic variant among human geneticists, but we use the term mutation throughout the manuscript for the sake of expediency. Associated references are provided in **Supplemental Table 4**; references for additional proposed CVID genes are listed in **Supplemental Table 5**. For a discussion of molecular diagnostic strategies as well as functional triage and validation of potential CVID-related variants, see recent reviews (7, 8).

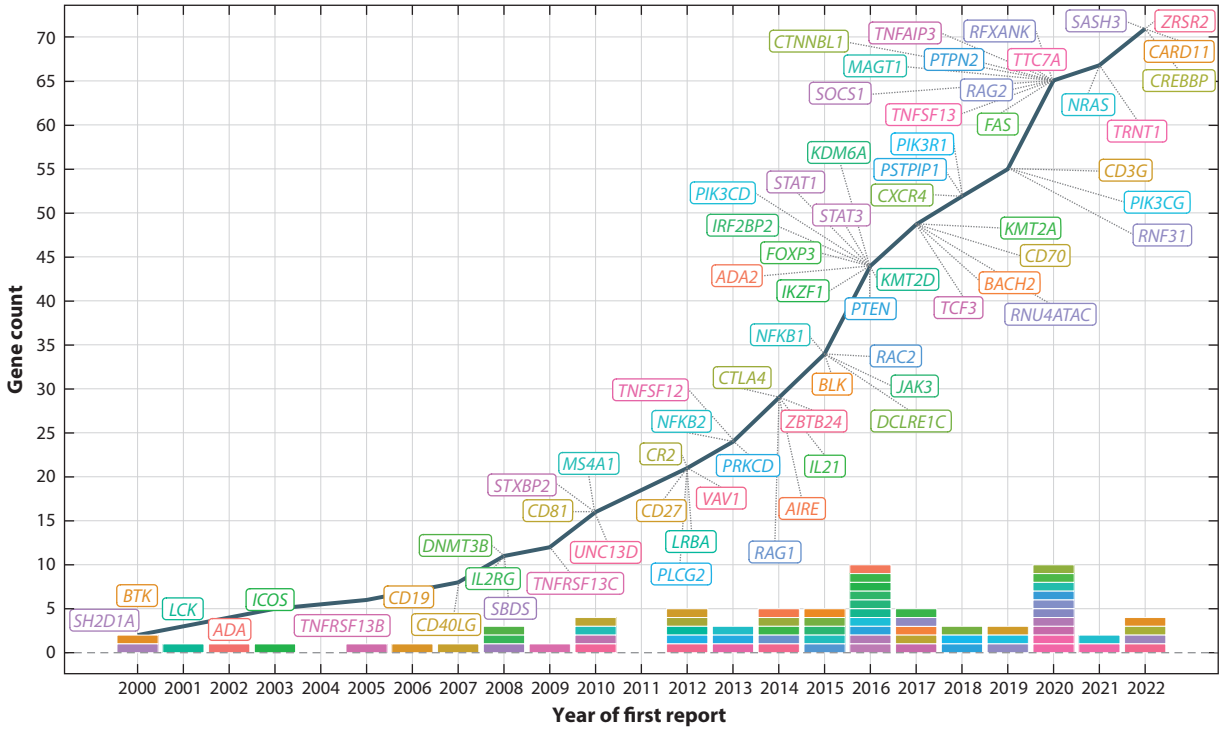

Figure 3

Newly reported common variable immunodeficiency (CVID) and CVID-like genes over time. Genes ($n = 71$) are shown in chronological order of their first appearance in a publication in association with an individual with a CVID phenotype.

3.1. Predominantly Antibody Deficiencies Associated with CVID Phenotypes

Not surprisingly, many of the early monogenic forms of CVID identified mutations in key genes involved in B cell survival, proliferation, development, maturation, and function (**Table 1**). These include key developmental transcription factors (TFs) driving various stages of B cell differentiation; enzymes required for generating a diverse BCR repertoire and isotype switching; and cell surface and signal transduction proteins that fine-tune this repertoire in response to antigenic and tolerance cues.

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3.1.1. B cell receptor costimulatory B cell surface proteins. Mutations in four genes encoding key BCR costimulatory proteins (*CD19*, *MS4A1/CD20*, *CR2/CD21*, and *CD81*) have each been identified in a few CVID patients (**Figure 4**; **Supplemental Table 4**). Peripheral B cell counts are usually normal, reflecting preserved B cell development, but patients are hypogammaglobulinemic with impaired vaccine responses due to defects in terminal B cell activation or affinity maturation. This emphasizes the importance of BCR costimulation for optimizing humoral responses to specific antigens in B cell germinal center (GC) reactions.

3.1.2. Tumor necrosis factor superfamily receptors and ligands. Interactions between lymphocyte-specific tumor necrosis factor superfamily (TNFSF) ligands (i.e., TNFSF13B/TALL1/BAFF/BLYS, TNFSF13/APRIL, and TNFSF12/TWEAK) and receptors (i.e., BAFF-R, TACI, and BCMA) (**Figure 2**) also play crucial roles in terminal B cell maturation, survival, and function. The receptor-ligand interactions are specific but also partially redundant and

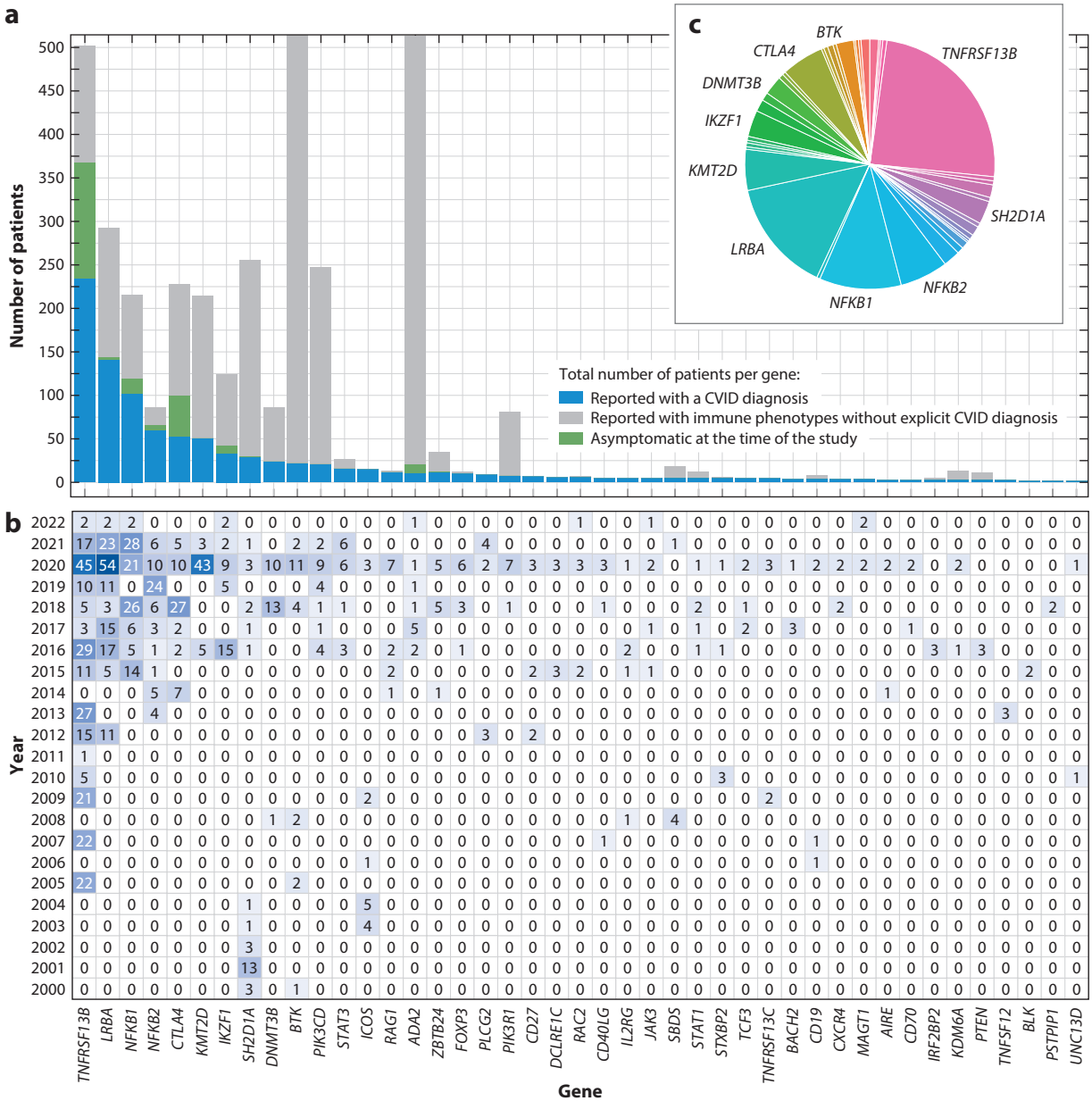

Figure 4

Number of reported common variable immunodeficiency (CVID) and CVID-like patients in original publications per gene ($n = 43$) over time. (*a*) Total number of patients per gene (showing 500 max) reported with a CVID diagnosis (*blue*), reported with immune phenotypes without explicit CVID diagnosis (*gray*), or asymptomatic at the time of the study (*green*). Papers that did not explicitly provide immunologic evaluation were excluded. An extensive literature search was completed for the first 10 genes shown in panel *b*, plus *ADA2*, *PIK3R1*, and *ZBTB24*. (*b*) Number of CVID patients per gene by year. (*c*) Relative proportion of CVID patients per gene, highlighting the top 10 genes. The following 28 genes were not plotted because only one or a few CVID patients were reported: *ADA*, *CARD11*, *CD3G*, *CD81*, *CR2*, *CREBBP*, *CTNNBL1*, *FAS*, *IL21*, *KMT2A*, *LCK*, *MS4A1*, *NRAS*, *PIK3CG*, *PRKCD*, *PTPN2*, *RAG2*, *RFXANK*, *RNF31*, *RNU4ATAC*, *SASH3*, *SOCS1*, *TNFAIP3*, *TNFSF13*, *TRNT1*, *TTC7A*, *VAV1*, and *ZRSR2*. Genes retrospectively associated with CVID (**Table 1**; **Supplemental Table 3**) by manuscripts other than the original publication are also excluded from the figure.

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complementary; for example, BAFF binds strongly to BAFF-R and TACI, but weakly to BCMA, while APRIL binds strongly to BCMA and weakly to TACI, but not to BAFF-R (9). Conversely, TACI binds both APRIL and BAFF with similarly high affinity and is essential for T cell–independent but not T cell–dependent B cell responses (10). Because of these complex interactions, it has been difficult to deconvolute their specific contributions to B cell maturation and function, but the identification of CVID-associated mutations (**Figure 4**; **Supplemental Table 4**) has contributed mechanistic insight.

TACI activation induces downstream activation of nuclear factor of activated T cells (NFAT), nuclear factor kappa B (NF-κB), and activator protein-1 family TFs to promote antibody production and plasma cell differentiation. Monoallelic or biallelic mutations in *TNFRSF13B*, the gene encoding TACI, are associated with CVID and sIgAD (11). Heterozygous *TNFRSF13B* mutations are specifically associated with autoimmune complications, due to the preservation of autoreactive B cell clones with residual responsiveness to T follicular helper (Tfh) cell stimulation (12). Predicted to act via dominant-negative (DN) or haploinsufficiency mechanisms, many mutations show incomplete clinical penetrance and are also found in asymptomatic individuals (~25% of mutation carriers) (**Figure 4**) with 0.5–0.7% allele frequencies in European populations, justifying their consideration as CVID risk alleles. Mutations such as C104R or A181E have been shown to result in little to no receptor signaling in both CVID patients and their asymptomatic relatives, highlighting divergence in cellular versus organismal penetrance (13). Carriers of these alleles who have no other affected family members show significantly lower risk of CVID development than those with just one affected family member; for the latter, a priori risk can be up to ~40% (Grimbacher lab, unpublished data). Taken together, these factors suggest that peripheral B cell tolerance can still be established despite defective central B cell tolerance checkpoints, with additional factors needed for disease development.

Loss-of-function (LOF) mutations in other TNFSF receptors and ligands also impair terminal B cell differentiation, survival, and function. *TNFRSF13C* encodes BAFF-R, which harbors both CVID-associated polymorphisms (**Supplemental Table 6**) and rare mutations causing B cell maturation arrest at the transitional B cell stage (14). *TNFSF13* encodes APRIL, which heterotrimerizes with and shares overlapping receptors and functions with BAFF. One APRIL-deficient CVID patient showed progressive panhypogammaglobulinemia with significant marginal zone B cell expansion and markedly reduced blood plasmacytes, suggesting the importance of ongoing APRIL signaling for antigen-independent maintenance of plasmacyte populations (15). Finally, one *TNFSF12*/TWEAK mutation was proposed to cause CVID via a DN effect on downstream BAFF signaling, though effects on related ligands or receptors cannot be ruled out (16). Significantly more patient data are required to determine the degree of clinical penetrance and allelic effect exerted by variation in these genes.

3.1.3. Lipid signaling. Genetic defects in both phosphoinositide 3-kinase (PI3K) and PI4K signaling (**Figures 2** and **4**) have been linked to CVID, reflecting the importance of mTOR signaling for immune homeostasis.

Composed of constitutively associated catalytic and regulatory subunits, class I PI3Ks phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3), which recruits Pleckstrin homology domain–containing proteins such as AKT to activate mTOR signaling cascades directing cell survival, proliferation, differentiation, and cytoskeletal changes. Thus, p110δ-mediated signal transduction is important for naive $CD4^+$ T cell differentiation and T regulatory cell (Treg) homeostasis and function, as well as B cell development, proliferation, migration, and functions (17, 18).

Heterozygous gain-of-function (GOF) mutations in *PIK3CD*, which encodes p110δ, cause activated PI3K delta syndrome type 1 (APDS1) (17). These largely missense mutations result in inappropriately activated p110δ, leading to uncontrolled lymphocyte proliferation, accelerated T cell maturation and senescence, and impaired B cell maturation with aberrant responses to stimuli followed by self-destruction (19). Hyperactive PI3K signaling is also thought to interfere with GC structures by inhibiting class switch recombination (CSR), leading to an oft-observed HIGM-like phenotype, while B cell lymphopenia may be secondary to disrupted migration given the significant B cell proliferation seen in lymph nodes (20). Reflecting the many processes and cell types potentially affected by PI3K/AKT signaling, affected individuals can develop both humoral and cellular immunodeficiency, diverse autoimmune and autoinflammatory manifestations, and B cell malignancies (21). Similar presentations are seen for LOF mutations in *PIK3R1*, encoding the regulatory partner of p110δ; LOF mutations in *PTEN*, encoding a PIP3 phosphatase that counteracts PI3 kinase activity; or, interestingly, LOF of *PIK3CG*, encoding another leukocyte-predominant PI3K catalytic subunit, p110γ. Clinical and immune phenotypes can vary significantly for all forms of APDS, which can present as mild SCID (22), combined immunodeficiency (CID) (17), agammaglobulinemia (23), or HIGM syndrome (24, 25), in addition to CVID (**Supplemental Table 4**). Finally, *TTC7A* LOF causes defective PI4K signaling, which then impairs actin cytoskeletal dynamics and PI3K/AKT signaling. This leads to severe early-onset enteropathy and immunodeficiencies ranging from SCID to CVID (26), with antibody deficiency likely arising from both compromised gut integrity and lymphocyte-intrinsic defects. These conditions show that both too much and too little signaling can lead to B cell problems, highlighting the need to tightly regulate PI3K/AKT dynamics in response to stimuli.

3.1.4. Inborn errors of the actin cytoskeleton. A growing list of demonstrated (*CXCR4*, *RAC2*, *ARHGEF1*, *TTC7A*, and *PSTPIP1*) or proposed (*DOCK8* and *WAS*) CVID genes encode key regulators of actin dynamics (**Supplemental Tables 4 and 5**). CVID patients with ARHGEF1 deficiency teach us that impaired migration resulting in abnormal B cell distributions within GCs is only part of the story and that cytoskeletal changes are intimately connected to intracellular signaling. These patients' T and B cells show dysregulated AKT/mTOR signaling downstream of impaired RhoA GTPase function, further reinforcing the importance of this pathway in CVID pathogenesis. Mutations in *RAC2* are associated with three distinct but overlapping immunodeficiencies featuring defective neutrophil chemotaxis along with other variable immune defects. Both autosomal-recessive (AR) LOF (27) and autosomal-dominant (AD) GOF mutations (28, 29) can cause CVID-like phenotypes, while a single p.D57N missense mutation is associated with DN LOF (30, 31) without significant humoral defects. Unlike p.D57N, which preferentially binds GDP, GOF mutations favor the active GTP-bound state, resulting in prolonged activation of downstream effectors (29). The phenotypic convergence of these divergent mechanisms echoes the aforementioned need for dynamic feedback control of immune signaling.

Supplemental Material >

3.1.5. Transcription factors mediating differentiation and cross talk. TFs and their cofactors exert broad effects on immune cell gene regulatory programs, conferring the elasticity required to rapidly change states in response to diverse stimuli, as well as the plasticity to regain lineage identity and homeostasis. Because they often act on DNA in complex with other proteins and confer context-dependent repression or activation, it can be difficult to dissect specific mutational effects. The phenotypes associated with mutations in the TFs discussed below (**Figure 4**) span a broad (and variable) spectrum, depending on where and when in B cell development they are expressed, what roles they play in other cell types, and what other compensatory or buffering mechanisms are present. For example, while Ikaros family members are key developmental TFs

for hematopoietic lineages, the evolutionarily older NF-κB family plays broadly pleiotropic roles across immune and nonimmune cells.

IKZF1 encodes IKAROS, a tumor suppressor and key regulator of T and B cell differentiation, with specific roles in CSR and BCR expression for the latter. More than 110 individuals and at least five distinct published phenotypes are associated with various *IKZF1* mutational mechanisms (32–34). Of these, monoallelic LOF mutations have been linked to incompletely penetrant AD CVID in at least 29 patients (**Figure 4**; **Supplemental Table 4**). Despite a broad spectrum of onset and presentation, most patients develop recurrent bacterial respiratory infections associated with hypogammaglobulinemia, impaired vaccine responses, autoimmunity, and increased susceptibility to B cell malignancies. Almost all patients show severely reduced $CD19^+$ B cell counts, with markedly decreased pro-B cells and earlier precursors, while memory B cells are present. In contrast, early-onset CID due to DN *IKZF1* mutations additionally features T cell abnormalities with susceptibility to opportunistic viral and fungal infections. Though most CVID-associated mutations were thought to act by haploinsufficiency, the p.R143W mutation was subsequently shown to exert partial DN effects on DNA binding and pericentromeric heterochromatin localization (35, 36). Thus, given the complex functions and phenotypes associated with *IKZF1*, CVID may be linked to *IKZF1* mutations along a spectrum of DN and haploinsufficient effects, depending on the specific property being assayed.

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The five members of the NF-κB family—NF-κB1 (mature p50 and its precursor p105), NF-κB2 (mature p52 and its precursor p100), RelA/p65, RelB, and c-Rel—assemble into homo- and heterodimers to regulate gene expression in response to diverse stimuli. Inactive NF-κB precursors and NF-κB dimers bound to inhibitory proteins (IκBα, IκBβ, and IκBγ) are sequestered within the cytoplasm and remain transcriptionally inactive until stimulus-induced activation. This leads to phosphorylation and proteolytic processing of the p105 form of NF-κB1 into p50, which associates with RelA/p65 and is dissociated from IkBα via the latter's phosphorylation, polyubiquitination, and degradation. Upon release from its inhibitor, the p50/RelA heterodimer is then able to translocate to the nucleus for target gene transactivation. A similar process occurs for processing of NF-κB2/p100 into p52 as part of the noncanonical signaling pathway. Importantly, full-length p100 and p105 also antagonize p50-dependent DNA binding (37). Both canonical and noncanonical NF-κB pathways play key roles in B cell development and function.

Monoallelic *NFKB1* mutations are associated with AD CVID featuring defective B cell development and antibody deficiency along with a broad spectrum of autoinflammatory and immune dysregulatory phenotypes. Fliegauf et al. (38) reported the first 10 patients from three unrelated families, with the remaining carriers being asymptomatic with variable hypogammaglobulinemia. More than 200 individuals with *NFKB1* mutations have since been identified, with ~50% clinical penetrance for CVID but many given non-CVID diagnoses (**Figure 4**). Patients show hallmarks of autoinflammation such as increased interferon (IFN)-γ and TNF production in response to T cell stimulation, inflammasome hyperactivation, and interleukin (IL)-1β secretion from macrophages (39). *NFKB1* mutations may be the most common cause of AD CVID in Europeans and outbred populations (40, 41), but our meta-analysis suggests that AR LRBA deficiency is the most commonly reported monogenic cause of CVID overall.

Many initially identified NFKB1-deficient patients harbored N-terminal mutations that generated truncated, nonfunctional proteins, suggesting a haploinsufficiency mechanism (38). However, subsequent nonsense mutations also resulting in protein truncation exerted DN effects on nascent wild-type (WT) peptides, via binding, misfolding, and degradation of both (42). Some missense mutations cause haploinsufficiency by accelerating mutant p105 decay and disabling its processing into p50, reducing levels of both but preserving their activities and interactions (43). Others increase mutant p50 binding to NEMO, reducing nuclear entry (42) and likely also the pool of p50

homodimers promoting anti-inflammatory gene expression (44, 45). Given the complex layers of NF-κB regulation, pathogenic mechanisms have remained difficult to predict from the nature of the mutation alone. To address this issue, Li et al. (46) designed a functional assay for classifying *NFKB1* variants by their ability to activate NF-κB–mediated transcription in p65:p50 heterodimers while minimizing interference from p65:p65 homodimers. Applying this approach to 365 nonsynonymous *NFKB1* variants reported in CVID patients and healthy individuals, the authors identified 63 deleterious variants (19 hypomorphic). None showed DN effects and all were located in the N-terminal Rel homology domain important for dimerization, nuclear localization, DNA binding, and IκB interactions.

Mutations in *NFKB2* lead to AD CVID with penetrance similar to *NFKB1* mutations but are associated with fewer non-CVID diagnoses (**Figure 4**). Some C-terminal mutations result in truncated proteins lacking phosphorylation sites important for proteolytic processing of p100, resulting in repressive full-length p100 instead of activating p52—a DN effect (47, 48). Other C-terminal truncating mutations lead to increased nuclear accumulation of p52—a GOF effect. However, both types of mutations can lead to similar CVID phenotypes accompanied by autoimmunity, adrenal insufficiency, and/or ectodermal dysplasia (**Supplemental Table 4**). Finally, some C-terminal mutations also cause T and natural killer (NK) cell abnormalities (48–50), emphasizing roles for noncanonical NF-κB signaling beyond B cells. On the other hand, more upstream lesions, such as those within ankyrin repeats, are associated with antibody deficiency with few to no complications.

Supplemental Material >

3.1.6. Inborn errors of metabolism. CVID-like phenotypes have been reported for patients with congenital disorders of glycosylation (CDGs) and mitochondrial disorders (**Figure 4**; **Table 1**), highlighting the importance of metabolic regulation in immune cells.

MOGS LOF results in antibody deficiency from defective N-linked glycosylation, leading to the production of antibodies with much shorter half-lives (**Supplemental Table 3**). MAGT1 deficiency also causes defective N-glycosylation (51), but its regulation of $Mg2^{+}$ flux in T cells likely also contributes to B cell phenotypes (52). N- and/or O-linked glycosylation defects are also seen in CVID patients with X-linked *ATP6AP1* mutations (**Supplemental Table 3**) and in AR PGM3 deficiency, which is associated with hyper-IgE syndrome (HIES) and elevated—not reduced—levels of class-switched isotypes (53, 54). Thus, abnormal protein glycosylation may cause dysgammaglobulinemia through various mechanisms, from signaling or communication defects arising from abnormally modified surface proteins (i.e., CD19 and CD40) to impaired stability of secreted proteins. Finally, some patients present initially with sIgAD (55), suggesting the potential for more CDG mutations to be identified in those with sIgAD who eventually develop CVID (56).

Mitochondrial defects, particularly those associated with autoinflammatory and hematologic phenotypes in addition to adaptive immunodeficiency, are increasingly described in IEI patients with cellular evidence of replicative or metabolic stress. Interestingly, even though *TRNT1* encodes a ubiquitous transfer RNA nucleotidyltransferase, its LOF has been predominantly associated with humoral immunodeficiency (57, 58). Some patients have normal lymphocyte counts with preserved memory B cell proportions, while others show severe reductions in B cell and Tfh cell counts with evidence of pre–B cell maturation arrest, supporting the possibility of a metabolic checkpoint for B cells to proceed with further differentiation (also suggested by *FNIP1* mutations; see **Supplemental Table 3**). Yet others have progressively declining Ig and/or B cell counts over time (59, 60), suggesting survival and/or proliferation defects. B lineage cells rely on key bone marrow (BM) cues for their development and must rapidly activate high-volume protein production in

response to stimuli; thus, they may be more sensitive than other immune cell populations to both extrinsic inflammation and intrinsic defects in proteostasis and cellular stress tolerance (61). Supporting this idea are reports of CVID and/or predominantly antibody deficiencies in two patient populations typically associated with congenital neutropenia—Shwachman-Diamond syndrome due to *SBDS* mutations causing defective ribosome biogenesis (62, 63) and Barth syndrome due to *TAFAZZIN* mutations resulting in defective mitochondrial membrane dynamics (64).

3.2. Hypomorphic Mutations in Other Predominantly Antibody Deficiency Genes

Agammaglobulinemias are typically characterized by the complete lack of B cells in the periphery and thus absent immunoglobulins. However, some hypomorphic mutations in *BTK* and related B cell development genes (**Figure 2**) allow residual BCR signaling, with consequent survival of a small population of B cells and immunoglobulin production (65). These patients with less severe humoral defects may be diagnosed with CVID prior to molecular testing since CVID diagnostic criteria do not explicitly exclude severe B cell lymphopenia. Such a phenomenon is well documented for *BTK* mutations that lead to reduced mRNA expression and unstable and/or dysfunctional protein or are mosaically expressed (**Supplemental Table 4**). This is also increasingly seen for *TCF3* mutations and was recently reported for syndromic agammaglobulinemia due to mutations in *FNIP1* (**Supplemental Table 3**).

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Given the lack of specific criteria excluding abnormal IgM levels, CVID mutations are also recurrently identified in CSR genes classically associated with HIGM syndromes. Conversely, some genes typically associated with CVID may also engender HIGM phenotypes—for example, patients with inducible costimulator (ICOS) mutations are typically diagnosed with CVID, but ICOS deficiency in patient T cells impairs B cell CSR, leading to elevated IgM levels when B cells are activated during illness (66).

X-linked *CD40LG* mutations have been identified in multiple CVID patient cohorts (**Figure 4**; **Supplemental Table 4**). Similarly, a CVID-associated mutation was reported for *CTNNBL1*, encoding an integral spliceosome component that activates pre-mRNA splicing and participates in activation-induced cytidine deaminase (AID)-dependent CSR and somatic hypermutation (SHM) (67). This mutation interfered with CTNNBL1-AID binding, resulting in impaired nuclear translocation of AID and reduced SHM frequency. Interestingly, SHM frequencies are also severely reduced in the rare IgG^+ B cells isolated from CVID patients with autoimmune cytopenias relative to those without, accompanied by corresponding evidence of hyperplastic but inefficient GC reactions (67). This suggests that genetic lesions impairing CSR and SHM may predispose to the generation of autoreactive B cell clones and autoantibody production even in CVID patients lacking switched memory B cells, via cell-intrinsic mechanisms and/or signaling from autoreactive T cells. Interestingly, a germline homozygous mutation in *ZRSR2*, encoding another essential splicing factor, was recently reported for a CVID patient (68).

3.3. Diseases of Immune Dysregulation

In addition to predominantly B cell–intrinsic defects, defects in other immune compartments may also influence B cell homeostasis. This is especially true of T cell dysregulation, given the importance of cross talk between T and B cells at various stages of differentiation (**Figure 2**; **Table 1**). Indeed, many of the monogenic forms of CVID discussed above also show evidence of T cell dysfunction, despite their predominant associations with antibody deficiency. This highlights the importance of T effector cell repertoires for shaping B cell identities, especially the Tfh cells that orchestrate GC reactions and terminal B cell differentiation (69, 70).

3.3.1. Defective transcriptional regulation of central or peripheral tolerance. *AIRE* and *FOXP3* encode TFs critical for the two faces of immune tolerance. In medullary thymic epithelial cells, AIRE regulates the expression of diverse tissue-specific antigens from other lineages to select against autoreactive T cell clones, thus priming central tolerance. On the other hand, FOXP3 guards peripheral tolerance in its role as master regulator of Treg development and function. Although damaging mutations in both genes are classically associated with distinct syndromes featuring multisystem autoimmunity, some patients have been misdiagnosed with CVID. In the case of *AIRE*, the association has been reported not for biallelic APECED (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy) mutations but rather for heterozygous DN missense mutations in the SAND or PHD1 domains associated with more common, incompletely penetrant, later-onset organ-specific autoimmunities (**Supplemental Table 4**). In contrast, the X-linked *FOXP3* mutations reported are generally IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)-associated hypomorphic alleles (**Supplemental Table 4**). In these patients, defective CSR and memory B cell generation arise secondary to expansion of dysregulated Tfh cells showing T helper 1 (Th1) and Th17 skewing, like for other Treg-opathies. In addition, the observed expansion of autoreactive mature naive B cells suggests a potential defect in direct peripheral suppression, such as that mediated by T follicular regulatory cells (71).

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Unlike *AIRE* and *FOXP3*, mutations in *STAT3* lead to immune dysregulation via unrestrained, ligand-independent target gene activation. STAT3 is activated downstream of cytokine or mitogen signaling through nonreceptor tyrosine kinases (NRTKs) such as Janus kinase (JAK) or Src/mitogen-activated protein kinase (MAPK), which promote STAT3 phosphorylation, dimerization, and nuclear translocation. In immune cells, STAT3 regulates the expression of genes involved in cell survival and cytokine signaling, as well as naive T cell differentiation into specific Th subsets or Tregs.

Monoallelic *STAT3* mutations are associated with multiple somatic and germline disorders. CVID patients harboring germline GOF mutations show a broad spectrum of inflammatory and autoimmune phenotypes (**Figure 4**; **Supplemental Table 4**), while patients with DN LOF mutations develop AD HIES. STAT3 GOF complications are thought to partially arise from increased Th17 polarization, while STAT3 LOF complications are attributed to Th2 overpolarization at the cost of Th1 and Th17 lineages. Predominantly missense, the GOF mutations are distributed across important functional domains throughout the protein and may act via multiple mechanisms (72). For example, the p.K290N coiled-coil domain mutation found in one CVID patient led to increased in vitro transcriptional activity but also introduced a novel N-glycosylated motif (QNVSYK) promoting increased nuclear retention (73), a paradigm previously shown for other *STAT3* mutations (74).

While STAT3 is a key mediator of Th17 polarization, STAT1 favors the Th1 lineage, and both antagonize *FOXP3* expression in Tregs (75). Like STAT3, both too much and too little STAT1 signaling can lead to immune disease. Monoallelic and biallelic *STAT1* LOF mutations are associated with impaired IFN-mediated immunity, while *STAT1* GOF leads to chronic mucocutaneous candidiasis from impaired IL-17 immunity, as well as a CVID-like picture of antibody deficiency, infection susceptibility, and immune dysregulation. Similarly pleiotropic CVID presentations (26) have been reported for LOF in negative regulators of STAT1 signaling encoded by *SOCS1* and *PTPN2* (**Supplemental Table 4**). SOCS1 also harbors an E3 ligase function that contributes to pathogenesis via other pathways such as AKT/mTOR signaling (76).

Finally, *BACH2* haploinsufficiency (77) leads to CVID through disruption of a TF that regulates the balance between other TFs critical to T and B cell specification and maturation (78). Consistent with its importance for both Treg and terminal B cell differentiation, BACH2-deficient

patients have fewer Tregs, aberrant Th1 polarization, and impaired proliferation, as well as B cell maturation and CSR defects due to impaired Blimp1 repression (79).

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3.3.2. Membrane-bound organelle dynamics. Beginning with *CTLA4* and *LRBA*, mutations in a growing number of CVID-related genes (*SEC61A1*, *SH3KBP1*, *DEF6*, and *SAMD9*) (**Supplemental Table 3**) have highlighted the importance of membrane-bound organelle dynamics for both adaptive and innate immunity. Dysfunction in some genes leads to protein trafficking defects with consequences for ER homeostasis or control of receptor signaling, while others may affect calcium flux or mitochondrial health. Patients show diverse combinations of immunodeficiency, autoimmunity, and autoinflammation, with variable myeloid and syndromic defects.

Treg-mediated suppressive activities rely on FOXP3-dependent activation of immune checkpoint genes such as *CTLA4* and repression of other genes favoring Th cell activation and expansion. *CTLA4* encodes a receptor that is constitutively expressed in Tregs cells but is upregulated in conventional T cells only after activation for negative feedback regulation of immune responses (80). CTLA-4 antagonizes CD28-dependent costimulation by removing the ligands they share (CD80 and CD86) from antigen-presenting cells (APCs) via transendocytosis to dominantly suppress APC-mediated Th cell activation (81).

CTLA-4 deficiency is characterized by recurrent infections, hypogammaglobulinemia, and multiple autoimmune complications, including enteropathy and interstitial lung disease. Unlike LRBA deficiency (discussed below), it shows approximately 75% clinical penetrance overall, but only approximately one-third of affected individuals have CVID diagnoses (**Figure 4**; **Supplemental Table 4**). Though haploinsufficiency is considered the predominant mechanism, some ligand-binding domain mutations exert a DN effect on CTLA-4–CD80/86 interactions. Relative to *CTLA4* WT controls, both affected and unaffected carriers show increased T cell activation and expansion of Tregs with impaired suppressive functions, reduced CTLA-4 ligand binding abilities, and defective CD80 transendocytosis. This corresponds to expansion of $CD21^{low}$ and autoreactive B cell populations, increased B cell apoptosis, and poor BCR-induced proliferation, similar to observations in IPEX patients. Thus, CTLA-4 defects reduce B cell tolerance and survival through both loss of T cell–mediated suppression and inappropriate gain of T cell activation, in addition to potential B cell–intrinsic defect(s).

Similarly, *LRBA* mutations leading to functional CTLA-4 loss have been identified in ~140 patients, with robust clinical penetrance but non-CVID-like diagnoses in up to 50% of affected individuals (**Figure 4**; **Supplemental Table 4**). Clinical presentations overlap significantly with those of CTLA-4 deficiency, but LRBA patients develop infections at an earlier age, and in advance of or concomitantly with autoimmune findings, while the former tend to develop autoimmunity first and infections later, potentially explaining their greater delay in diagnosis (82). Some patients may not develop CVID until after receiving rituximab to treat their autoimmune manifestations (83), highlighting the fact that anti-CD20 biologics may uncover monogenic IEIs in some who develop persistent hypogammaglobulinemia after treatment. Most patients show low Treg, switched memory B cell, and plasmablast levels (84, 85), consistent with the observations that LRBA-deficient B cells cultured under favorable conditions fail to develop into antibody-secreting plasmablasts and show increased susceptibility to apoptosis (84). Moreover, these B cells show abnormal organellar accumulation and reduced LC3 localization to lysosomes, suggesting an LRBA-mediated autophagy defect (86). In 2015, Lo et al. (87) identified CTLA-4 as a key protein whose trafficking is regulated by LRBA. They found that LRBA colocalized with CTLA-4 in endosomal vesicles, that LRBA LOF increased CTLA-4 turnover, and that inhibiting lysosomal degradation prevented CTLA-4 loss in LRBA-deficient cells. Moreover, patients with LRBA deficiency show defective transendocytosis consistent with secondary CTLA-4 LOF (88). Finally, the

dramatic response of LRBA-deficient patients to abatacept, a CTLA-4-Ig fusion drug, reinforced this mechanistic relationship and suggested shared therapeutic approaches for both conditions.

3.3.3. Lymphoproliferative conditions. Mutations in a variety of genes typically associated with T cell–driven lymphoproliferation have been reported for CVID patients in case reports and large NGS cohorts (**Figure 4**; **Supplemental Table 4**). They are associated with conditions that share key clinical features with CVID, including recurrent infections, hypogammaglobulinemia, splenomegaly, lymphadenopathy, and autoimmunity. Some genes lead to CIDs complicated by EBV susceptibility such as *CD27*, *CD70*, *MAGT1*, *SH2D1A*, and *PRKCD*. Others such as *FAS* or *FASLG* are associated with autoimmune lymphoproliferative syndromes (ALPS), which share both clinical and immunophenotypic findings with CVID. Examples of the latter include expansion of transitional B cells with concomitant reduction in marginal zone B cells, switched memory B cells, and plasmablasts (89). Finally, mutations in *STXBP2* or *UNC13D* are typically associated with familial hemophagocytic lymphohistiocytosis but may be mistaken for CVID when hypogammaglobulinemia and reduced memory B cells are present; $CD8^+$ T and NK cell defects can be more subtle with delayed clinical presentations (90, 91).

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3.4. Combined Cellular and Humoral Immunodeficiencies

CIDs, including various forms of SCID, are often misdiagnosed as CVID (**Table 1**) when clinical evidence of cellular immunodeficiency is subtle or later onset, revealed only through detailed serial immunophenotyping. Indeed, the observation that late-onset CID develops in a subset of CVID patients with higher prevalence of lymphoproliferative disease and other T cell–driven comorbidities (92) suggests that some of these patients harbor monogenic disease.

With increasing molecular diagnosis, the phenotypic spectrum for many classic SCID genes has expanded to include immunodeficiencies of varying severities (93), from classic SCID to attenuated SCID to CID to CVID (**Figure 4**; **Supplemental Table 4**), often associated with autoimmunity (94) and/or autoinflammation (95). This has been shown for *ADA*, encoding intracellular adenosine deaminase, for genes involved in IL-2 signal transduction such as *IL2RG* and *JAK3*, and for key V(D)J recombination genes such as *DCLRE1C*, *RAG1*, and *RAG2*. As for the agammaglobulinemias, mutations associated with CVID-like phenotypes may confer enough residual expression and/or activity to permit some T cell development or to be mosaically expressed (96, 97).

DN mutations in *CARD11*, encoding a key signal transducer of NF-κB signaling downstream of TCR and BCR activation, are typically associated with Th2-polarized HIES-like CID, but at least one patient has been diagnosed with CVID prior to molecular testing (98). Similarly, a CVID diagnosis prior to recognition of CID was recently reported for a patient with X-linked deficiency in *SASH3*, encoding another key scaffolding/adaptor protein for T and B cell signaling (99).

Finally, emerging evidence suggests that mismatch repair genes (*PMS2* and *MSH5*) may contribute to CVID pathogenesis through roles in CSR and SHM (**Supplemental Tables 4–6**), further expanding the complex network of DNA damage repair modalities participating in recombination.

3.4.1. T cell signaling. *ICOS* was first linked to CVID by Grimbacher and colleagues (100, 101), who identified homozygosity for a shared founder deletion that abrogated protein expression in the T cells of nine affected individuals from four families. This gene encodes a T cell costimulatory receptor from the same family as CD28 and CTLA-4 (102) whose unique ligand ICOS-L is expressed on APCs such as naive B cells (103). ICOS contributes to B cell proliferation and differentiation into memory and plasma cells by promoting Tfh cell differentiation and survival and IL-10 production (104–106). The genotype and phenotype spectrum has since expanded

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(**Supplemental Table 4**), with patients presenting across all ages and with all possible complications on the CVID spectrum. Shared immunophenotypic features include hypogammaglobulinemia with variable IgM levels, absent isotype-switched vaccine responses, and reduced switched memory B cells but often normal total and naive B cell populations. Though ICOS is almost exclusively expressed on activated T cells, some patients have largely normal T cell subsets and responses to mitogen stimulation. Others show more obvious deficits including reduced memory T cells, impaired Th and Treg cytokine production, and reduced induction of Th lineage–specifying TFs such as T-bet, GATA3, MAF, and RORC (107). Moreover, *FOXP3* and *CTLA4* expression, as well as Treg levels, may be reduced in conjunction with autoimmune and inflammatory features.

Mutations in additional CID genes important for T cell priming, activation, or signaling have been identified in CVID patients (**Supplemental Table 4**). These include *CD3G*, encoding a subunit of the TCR-CD3 complex that couples antigen recognition to downstream signaling, and Src family NRTKs *LCK*, *ZAP70*, and *SYK* (**Supplemental Table 3**). In particular, LCK LOF shows a spectrum of severity from SCID (108) to T cell–predominant CID (109, 110) to CVID with defective B cell CSR (109). A mutation was also reported in *RFXANK*, encoding a subunit of the key transcriptional regulator of major histocompatibility complex class II genes. Finally, IL21 and IL21R LOF patients presenting with CVID-like phenotypes (**Supplemental Table 3**) often show more subtle signs of cellular immunodeficiency, such as aberrant T cell cytokine production or impaired NK cell cytotoxicity, in addition to reduced memory B cells and defective CSR.

3.4.2. Inborn errors of epigenetic regulation. As mentioned above, significant epigenetic alterations have been identified in the immune cells of CVID patients relative to healthy controls. Unsurprisingly, CVID-associated mutations (**Figure 4**) have been identified in DNA and histone methylation/demethylation enzymes that modulate the broad transcriptional changes required for stepwise lineage specification and fate restriction during development (**Figure 2**).

The Ig heavy chain (IgH) locus specifically undergoes a series of gene regulatory changes during B cell differentiation, first for promoting CSR and then again for SHM (111). In activated naive mature B cells, markers of open chromatin accumulate throughout the V(D)J and IgH switch regions, initiating a cascade of additional chromatin modifications and *trans*-factor recruitment culminating in recombination. Written by lysine methyltransferases such as KMT2D/MLL2, the H3K4me3 modification is associated with open chromatin and transcriptional activation, while H3K27me3 is a modification associated with facultatively closed chromatin whose removal by lysine demethylases such as KDM6A/UTX is equally necessary for establishing transcriptionally permissive chromatin.

Kabuki syndrome was linked to CVID-like humoral defects (112) and autoimmune complications (113) even before the identification of causative genes *KMT2D* and *KDM6A*. In addition to reduced memory T cell populations, patients with *KMT2D* mutations show evidence of impaired terminal B cell differentiation, with significantly reduced memory and switched memory B cells and expanded $CD21^{low}$ B cells. Furthermore, patient B cells show significantly impaired SHM and a subset with C-terminal missense mutations show greater autoimmune tendencies, potentially due to accumulation of autoreactive B cell clones (114). The immunophenotype of KDM6A LOF is less well characterized, but one patient had normal total and memory B cell levels, consistent with his later-onset, milder CVID (115). However, he also carried a heterozygous *TNFRSF13B* risk variant that may have been contributory. Similarly, patients with Wiedemann–Steiner syndrome, due to monoallelic *KMT2A* mutations, have also been reported with CVID diagnoses (178).

Immunodeficiency-centromeric instability-facial anomalies syndrome (ICFS) was also linked to CVID prior to identification of causative genes (116), but germline mutations in *DNMT3B*

and *ZBTB24*, associated with ICFS1 and ICFS2, respectively, have since been identified in multiple CVID patients (**Supplemental Table 4**). *DNMT3B* encodes a key somatic de novo DNA methyltransferase, while *ZBTB24* encodes a transcriptional repressor important for juxtacentromeric DNA methylation (117). ICFS is characterized by heterochromatin-associated methylation defects, leading to pathognomonic multibranched chromosomal configurations arising from increased somatic recombination in stimulated lymphocytes. Patients show a broad spectrum of immunodeficiencies ranging from hypogammaglobulinemia or agammaglobulinemia to, less commonly, CID (118, 119) and SCID (120). Patients have increased immature B cell populations with reduced memory B cell numbers and show retention of autoreactive clones, inverted CD4/CD8 ratios, and increased susceptibility of T and B cells to activation-induced apoptosis (121, 122). This may explain why some ICFS2 patients begin with grossly normal immunophenotypes but subsequently evolve CID with autoimmunity (123). Humoral immunodeficiency may be more pronounced in ICFS1 than ICFS2 patients, though both show T and B cell abnormalities (118). ICFS1 patient-derived lymphoblastoid cell lines show gene expression changes and promoter hypomethylation at key immune loci that also lose normally repressive histone modifications and gain activating chromatin marks (124). This is consistent with well-known recruitment of repressive chromatin-modifying complexes to methylated CpG DNA (125) and preferential binding of activating complexes to unmethylated CpG DNA (126). ICFS2 cells are additionally defective in α-satellite methylation, though the clinical implications of this remain unclear (127).

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Patients with Rubinstein-Taybi syndrome, due to mutations in transcriptional coactivator CREBBP or histone acetyltransferase EP300, also develop humoral immunodeficiency with autoimmune or inflammatory complications, manifesting as CVID- and ALPS-like presentations (128–130). Of note, mice expressing B cell specific acetyltransferase-deficient p300 die prematurely from SLE-like disease with abnormal mature B cell responses, further highlighting the importance of ongoing transcriptional control for maintaining B cell self-tolerance (131).

3.5. Autoinflammatory Disorders

Defective innate immunity and autoinflammation are emerging as features of many immunodeficiencies traditionally thought of as adaptive immune disorders, such as ataxia telangiectasia or Artemis/*DCLRE1C* deficiency (95). Similarly, gene expression studies are finding evidence of innate immune activation in CVID patients (132). Furthermore, an increasing burden of germline mutations associated with diverse systemic autoinflammatory disorders has been found in CVID patients (**Figures 2** and **4**). Many of these genes serve important functions across multiple tissue types with extensive immune cross talk, so they likely contribute to B cell dysfunction through both cell-intrinsic and non-cell-intrinsic mechanisms (**Figure 2**). As mentioned above, one mechanism directly links impaired B cell development and plasma cell survival to chronic BM inflammation (133), while others implicate dysregulated signal transduction pathways downstream of B cell activation.

AR ADA2 LOF accounted for up to 6% of mutations in one large CVID patient cohort (133) and is recurrently seen in CVID patients (**Figure 4**; **Supplemental Table 4**). Primarily expressed by myeloid and endothelial cells, *ADA2* encodes a secreted adenosine deaminase thought to act on extracellular adenosine pools. Deficiency of ADA2 (DADA2) polarizes macrophages toward an M1 inflammatory type, activates neutrophils, and triggers type 1 IFN activation, resulting in diverse inflammatory symptoms including vasculitis. However, ADA2 likely also plays enzyme-independent roles in cell proliferation and differentiation, contributing to its broad spectrum of immunodeficiencies and BM insufficiencies. A minority of DADA2 patients with milder or later-onset inflammatory or hematopoietic findings may be mistakenly diagnosed with CVID, or sIgAD evolving into CVID (134–136), but even the majority of those without CVID diagnoses show

humoral defects associated with CVID-like immunophenotypes, including significantly reduced memory and switched memory B cells, expanded CD21^{low} B cells, reduced Tregs, and increased Tfh cells showing impaired IL-21 production (137, 138).

The linear ubiquitination chain assembly complex (LUBAC) is a heterotrimeric E3 ligase complex (HOIP, HOIL-1, and SHARPIN) that adds linear polyubiquitin chains to stabilize key inflammatory receptor signaling complexes after activation (139). LUBAC is important for CD40-dependent activation of B cells and plays a key role in IκB kinase complex activation via NEMO polyubiquitination (140). CVID patients have been found with mutations in *RNF31*, which encodes HOIP, the catalytic component of LUBAC (141). Conversely, *TNFAIP3* encodes A20, which reverses the effects of polyubiquitination to downregulate NF-κB signaling and TNF-mediated apoptosis using its ubiquitin-ligase and deubiquitinase activities. Though generally presenting with severe pancytopenia, inflammatory, and autoimmune findings, A20 haploinsufficiency can also show milder CVID-like phenotypes (**Figure 4**; **Supplemental Table 4**).

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PLCG2 encodes PLCγ2, which catalyzes the hydrolysis of PIP2 into secondary messengers diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) downstream of BCR activation. IP3 signals via $Ca2^{+}$ calmodulin to activate NFAT family members, while DAG signals via protein kinase C to activate RAS/MAPK signaling. PLCG2 mutations are associated with two AD conditions that may be mistaken for CVID on the basis of variable antibody defects—FCAS3 (familial cold autoinflammatory syndrome 3) and APLAID (autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation). FCAS3 patients harbor large autoregulatory domain deletions leading to gain of enzymatic function but loss of distal signaling and PLCG2-dependent downstream functions. Unsurprisingly, activated patient B cells show defective $Ca2^{+}$ flux and BCR signaling responses. In contrast, APLAID patients carry heterozygous missense GOF mutations resulting in constitutive enzyme activation (142) and dysregulated NLRP3 inflammasome activation (143). Of note, potentially disease-causing variants in other inflammasome signaling genes (i.e., *NLRC3*, *NLRC4*, *NLRP2*, *NLRP3*, and *NLRP12*) have also been reported in CVID patients (**Supplemental Table 5**). The above mechanisms again highlight the Goldilocks principle that similar immune problems can arise from too much or too little amplitude, frequency, or duration of signaling.

4. OTHER INHERITANCE MODELS

4.1. Oligogenic CVID: Epistasis Versus Additivity

Given the significant overlap of clinical phenotypes across IEIs, not to mention extensive cross talk and mechanistic overlap, distinguishing truly epistatic effects from additive or blended effects conferred by multiple variants can be challenging (144, 145). Epistasis has been reported for CVID-related genes in the context of other phenotypes (146, 147), but few digenic interactions have been specifically reported for CVID patients, with some more likely to be additive than epistatic (**Supplemental Table 7**). Thus, beyond the risks contributed by a few alleles (i.e., *TNFRSF13B* variants), oligogenic models of CVID remain poorly understood, including how common and rare IEI variants interact on the background of specific HLA haplotypes.

4.2. Polygenic CVID: Risk Loci Identification Through Genome-Wide Association Studies

Above, we discussed mutations in genes such as *TNFRSF13B* that confer increased but incompletely penetrant susceptibility to the development of CVID-like phenotypes. However, much less is known about the pathophysiological roles of other loci with relatively high allele frequencies that confer low individual levels of risk, especially those without previously delineated immune

functions. Such loci have mainly been identified through GWAS over the last 15 years and are summarized in **Supplemental Table 6**. Some are found within genes (i.e., *CTLA4* and *TNFRSF13C*) or pathways (i.e., cell-cell communication, DNA damage repair, and mitochondrial health) already implicated in CVID pathogenesis, while others (i.e., ciliary signaling and pre-mRNA splicing) suggest emerging immune-relevant processes that demand further exploration.

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5. GENE DOSAGE VARIATION

5.1. Structural and Copy Number Variation

The original 1999 European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency diagnostic criteria listed four chromosomal anomalies as differential diagnoses to be excluded (148), anticipating now well-known associations such as that between chromosome 18q− deletion and sIgAD/CVID (149). Structural variants (SVs) and copy number variants (CNVs) frequently affect some CVID-related loci and show emerging relevance to CVID pathogenesis (**Supplemental Table 8**), but few causative examples have been identified in CVID patients due to the limitations of current short-read NGS platforms (150). Though improved yields have been achieved through the use of additional approaches such as targeted sequencing (151), digital droplet polymerase chain reaction (152), exon-tiling arrays (153), or whole-genome sequencing (WGS) (26), some loci with true pathophysiological relevance almost certainly remain underrepresented in the current CVID gene space, especially if harboring sequence degeneracy like *IKBKG* (encoding NEMO); indeed, we recently identified an *IKBKG* mutation in a patient treated for CVID (X.P. Peng, unpublished data). With its detection advantages, improved bioinformatics, decreasing costs, and increasing accessibility, WGS may soon be preferred to exome sequencing for upfront clinical diagnosis of heterogeneous immunodeficiencies such as CVID. The eventual optimization of long-read NGS for clinical use may further improve SV and CNV detection, but all discovery efforts remain stymied by an inadequately diverse and representative reference genome (154, 155).

5.2. Somatic Variation

Similarly, though somatic mutations that can phenocopy (or rescue) IEIs have been well described in the literature for many genes, somatic variation in CVID is just beginning to be explored (**Supplemental Table 8**). One study identified recurrent somatic changes in the T cells of CVID patients with autoimmunity and lymphoproliferation (156), indicating that clonal T cell populations may influence B cell behaviors, leading to specific clinical complications. Many examples of somatic mosaicism are known for CVID-related genes, but few have been identified in CVID patients. The latter includes reversion mutations that attenuate germline LOF severity (97, 157) and a somatic *NRAS* GOF mutation engendering an ALPS-like condition diagnosed as inflammatory CVID (158). As for other immune dysregulatory CVIDs, patients may be hypergammaglobulinemic prior to becoming antibody deficient—a clue that may help distinguish these etiologies from those of primary B cell failure in patients who eventually converge on a CVID-like phenotype.

6. CONCLUSION

In summary, technological advances over the past decade have significantly augmented our understanding of the diversity of genotypes and phenotypes associated with the term CVID. Improved immunophenotyping and functional studies have identified recurrent abnormalities in the immune cell populations and features of CVID patients, while increased sequencing has expanded the repertoire of pathways contributing to CVID and also added CVID to the phenotypic spectrum

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of known Mendelian IEIs. Our currently known CVID genetic landscape encompasses diverse biological processes (**Figure 2**; **Supplemental Figure 2**) and virtually every IEI category (**Table 1**).

However, many unanswered questions remain. We have barely begun to describe how different CVID-related loci interact, though the vast majority of patients likely have oligogenic or polygenic disease. We continue to struggle with limits of detection for gene dosage and regulatory sequence contributions to pathogenesis, while additional genetic paradigms likely remain unelucidated for CVID. We have mounting evidence for metabolic and epigenetic contributions to CVID pathogenesis, but the origins and effects of these changes remain unclear. We have evidence that antigen engagement and responses are often altered in CVID, but we have barely begun to connect environmental influences to specific CVID complications. Information gained from genotyping may have less value without the context provided by such orthogonal knowledge, just as integration of large omics datasets cannot supplant lessons learned from in-depth mechanistic examination of single cases. As no single strategy has proven sufficient for capturing the complex heterogeneity of CVID, value remains in developing a pluralistic approach to representing each patient's unique pathophysiology.

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