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Immunological loss-of-function due to genetic gain-of-function in humans: autosomal dominance of the third kind

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Abstract

All the human primary immunodeficiencies (PIDs) recognized as such in the 1950s were Mendelian traits and, whether autosomal or X-linked, displayed recessive inheritance. The first autosomal dominant (AD) PID, hereditary angioedema, was recognized in 1963. However, since the first identification of autosomal recessive (AR), X-linked recessive (XR) and AD PID-causing genes in 1985 (*ADA*; severe combined immunodeficiency), 1986 (*CYBB*, chronic granulomatous disease) and 1989 (*SERPING1*; hereditary angioedema), respectively, the number of genetically defined AD PIDs has increased more rapidly than that of any other type of PID. AD PIDs now account for 61 of the 260 known conditions (23%). All known AR PIDs are caused by alleles with some loss-of-function (LOF). A single XR PID is caused by gain-of-function (GOF) mutations (WASP-related neutropenia, 2001). In contrast, only 44 of 61 AD defects are caused by LOF alleles, which exert dominance by haploinsufficiency or negative dominance. Since 2003, up to 17 AD disorders of the third kind, due to GOF alleles, have been described. Remarkably, six of the 17 genes concerned also harbor monoallelic (*STAT3*), biallelic (*C3*, *CFB*, *CARD11*, *PIK3R1*) or both monoallelic and biallelic (*STAT1*) LOF alleles in patients with other clinical phenotypes. Most heterozygous GOF alleles result in auto-inflammation, auto-immunity, or both, with a wide range of immunological and clinical forms. Some also underlie infections and, fewer, allergies, by impairing or enhancing immunity to non-self. Malignancies are also rare. The enormous diversity of immunological and clinical phenotypes is thought provoking and mirrors the diversity and pleiotropy of the underlying genotypes. These experiments of nature provide a unique insight into the quantitative regulation of human immunity.

Introduction

Over the last 30 years, the analysis of various immunological and clinical phenotypes in humans has revealed the even greater genetic diversity of monogenic PIDs, as herein arbitrarily defined as single-gene inborn errors of immunity, not necessarily displaying complete clinical penetrance [1,2]. PIDs can manifest in various combinations of phenotypes, which belong in five broad categories, infection, malignancy, allergy, autoimmunity, and autoinflammation (Figure 1). The number of genetically defined PIDs has increased from 105 to 260 in the last 10 years alone [2,3], and is expected to increase further, with the rapid increase in next-generation sequencing use [4–6]. Over the same period, the number of AD traits increased from 14 to 61 (an approximate 4-fold increase), a much larger increase than for AR (79–188, 2.5-fold) and XR disorders (13–17, 1.3-fold). Most AD PIDs are caused by LOF alleles (44 defects), whether null (complete lack of function, not necessarily by loss of gene product expression) or hypomorphic (residual function, requiring residual expression of the gene product), and by mechanisms more frequently involving negative dominance (the mutant allele reducing the function of the WT allele product, 30 defects) than haploinsufficiency (the WT allele product functioning normally, 14 defects) [7]. Interestingly, since 2003 [8•], 17 AD disorders have been shown to be caused by GOF alleles (Table 1). In theory, GOF alleles can be hypermorphic (increase in normal function) or neomorphic (acquisition of a new function). As all known GOF mutant alleles underlying PIDs are hypermorphic, we will use GOF to cover these two expressions indiscriminately. Almost all AD PID-causing GOF mutant alleles are missense. Only two of the 17 genes sometimes also harbor nonsense mutations, which are, surprisingly, GOF (*NFKBIA* and *CXCR4*) or, in only one case, an in-frame deletion (*PLCG2*). For six genes (*C3*, *CFB*, *STAT1*, *CARD11*, *STAT3*, and *PIK3R1*), LOF mutant alleles have been described in patients with other clinical phenotypes, AR, AD, or both. Only mutations of *STAT1* have been shown to cause AR PIDs by LOF and AD PIDs by LOF or GOF [9]. We are aware of only one X-linked gene, *WASP*, able to harbor both LOF and GOF mutations, underlying XR WAS and XR neutropenia (which is not X-linked dominant due to skewed X-inactivation), respectively [10–12]. GOF mutations of *WASP* were first described in 2001 [10], before the first demonstration of a GOF underlying an AD PID in 2003 (mutation in $\text{IkB}\alpha$) [8•]. We review here the 17 AD GOF PIDs, as this topic is emerging and makes an original contribution to the fields of fundamental and clinical immunology (Table 1) [2,13]. These heterozygous GOF mutations disrupt various immunological functions and often result in various forms of autoinflammation, autoimmunity, or, more rarely, infection. Allergies and malignancies are even more rare. Their clinical penetrance is typically high, often complete. Accordingly, they can be caused by *de novo* mutations, the proportion of which and that of sporadic and familial cases depending on the impact of the disorder on reproduction. We have somewhat arbitrarily classified these conditions into five phenotypic categories (Figure 1). Because these conditions are rarely considered as PIDs, we arbitrarily excluded from this review inborn errors of osteoclasts, such as cherubism, osteolysis, and osteopetrosis, although GOF mutations of *SH3BP2* were shown to cause cherubism [14–17].

Autoinflammation without autoimmunity, allergy and infection

Heterozygous GOF mutations have been reported in some AD conditions characterized by the most typical clinical features of autoinflammation, such as recurrent fever, skin, joint and muscle symptoms, which are associated with a hyperactive inflammasome, enhanced inter-leukin (IL)-1 production and clinical response to anti-IL-1 treatment. In this category, we find the Cryopyrin-Associated Periodic Syndromes (CAPS) and Pyogenic sterile Arthritis, Pyoderma gangrenosum, and Acne (PAPA). In related patients with *NLRP3* mutations, early-onset autoinflammation is apparently associated with macrophage activation syndrome. In addition, GOF mutations were found in patients with conditions that are not associated with the most typical clinical features of autoinflammatory diseases, mainly affect one or few organs, do not necessarily respond to anti-IL-1 treatment but share with the first group of conditions a deregulation of innate immunity activation: Pediatric granulomatosis due to *NOD2* mutations, some atypical hemolytic uremic syndromes and a few cases of psoriasis associated with *CARD14* mutations.

Cryopyrin-associated periodic syndromes (CAPS) comprise three related, allelic entities characterized by intermittent episodes of rash, arthralgia, fever and conjunctivitis: familial cold autoinflammatory syndrome (FCAS; OMIM# 120100), Muckle-Wells syndrome (MWS; OMIM# 191900), and chronic infantile neurologic, cutaneous and articular disease, also known as neonatal onset multisystem inflammatory disease (CINCA/NOMID; OMIM#607115). In MWS and CINCA/NOMID, patients may also develop deafness, uveitis, papillitis. CINCA/NOMID patients have a very early onset of disease, with chronic, aseptic, neutrophilic meningitis and, in some cases, pseudotumoral cartilage bone hypertrophy. In 2001, mutations of *NLRP3* (*CIAS1*, *NALP3* and *PYPAF1*) were found in four families with FCAS or MWS [18•]. Other mutations of the same gene were reported in CINCA syndrome in 2002 [19]. *NLRP3* encodes cryopyrin, a cytoplasmic protein produced in myeloid cells that homo-oligomerizes upon activation (with exogenous ATP, K⁺ ionophore, [20]) and recruits ASC and procaspase-1 (forming the NLRP3 inflammasome). This leads to the autoproteolytic activation of procaspase 1 and the cleavage of pro-IL-1 β into IL-1 β . Specific mutations underlie FCAS or mild MWS, whereas others underlie severe MWS or CINCA, which are partly predicted by a three-dimensional model of the nucleotide-binding domain (NBD) of cryopyrin [21–26]. Somatic NLRP3 mosaicism has also been reported in CAPS patients, including patients with a severe CINCA phenotype [27]. Mutations affecting the NBD decrease affinity for cAMP in favor of Ca²⁺, one of the activators of NLRP3 inflammasome formation [28•]. Spontaneous IL-1 β secretion from peripheral blood mononuclear cells (PBMC) can be reversed by the activation of adenylate cyclase or the inhibition of phosphodiesterase-4, artificially increasing intracellular cAMP content and decreasing the constitutive assembly of the NLRP3-dependent inflammasome in the PBMC of patients [28•]. In the absence of known human LOF mutations, the GOF nature of the CAPS-causing *NLRP3* mutant alleles was established in 2009 on the basis of CAPS being reproduced in heterozygous and homozygous knock-in mice [29,30], but not in knockout mice [31]. Mouse and human *NLRP3*-mutated myeloid cells are hyperresponsive to signals that are normally ignored, leading to excessive leukocyte recruitment [25,30]. Perhaps the best illustration of the GOF nature of these alleles and the importance of in-

depth experimental studies of patients with PIDs is provided by the demonstrated efficacy of several anti-IL-1 biological agents in CAPS patients, leading to the adoption of these agents as the standard medical treatment [32–35].

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne disease (PAPA)

(OMIM#604416) manifests as episodes of sterile monoarticular arthritis in childhood, and later in life as pyoderma gangrenosum-like ulcerative skin lesions and cystic acne [36]. Mutations of *PSTPIP1* have been identified in patients with PAPA [37••]. *PSTPIP1* (also known as CD2BP1) is a cytoskeletal adaptor protein more strongly expressed in myeloid than in lymphoid cells, but not found elsewhere. *PSTPIP1* can interact, *via* its coiled-coil domain, with PTPN12, a Tyr-phosphatase, resulting in the phosphorylation of its Y344 residue [38]. It can also interact with WASP, c-Abl, and FasL [39]. *PSTPIP1* can also bind homotrimeric pyrin (also known as MEFV), which in turn recruits an ASC monomer, thereby forming an activated pyroptosome capable of processing pro-IL-1 β into IL-1 β [40]. GOF mutations lead to the hyperphosphorylation of *PSTPIP1* and an increase in its affinity for pyrin in overexpression systems, *via* an unknown mechanism leading to the constitutive ligation and activation of pyrin [40,41]. Adherent monocytes from one patient produced more IL-1 β than control cells following LPS stimulation [41]. In the absence of known human LOF alleles, the GOF nature of the mutants was inferred from the observation that transgenic heterozygous mice with an ectopically expressed human-derived mutant *Pstpip1* allele displayed auto-inflammation, whereas knockout mice did not [42]. The increase in the affinity of *PSTPIP1* for pyrin connects PAPA to familial Mediterranean fever (caused by AR-GOF mutations of the pyrin gene [43]), but the specific mechanisms underlying the overlapping and non-overlapping features of these two conditions remain largely elusive.

Early-onset autoinflammation and macrophage activation syndrome was recently reported in patients with *NRLC4* mutations [44,45]. Some patients displayed clinical, histological and immunologic features similar for many aspects to hemophagocytic lymphohistiocytosis (HLH) (OMIM#267700), which is characterized by severe early-onset autoinflammation caused by the massive infiltration of several organs with activated lymphocytes and macrophages, leading to fever, hepatosplenomegaly, cytopenia and, less frequently, central nervous system involvement [44,45]. A kindred has been reported to display FCAS (see below) [46••]. *NLRC4* is a ubiquitous, constitutively expressed cytoplasmic protein. It acts in cooperation with NAIP, the intracellular sensor of flagellin, and with components of the type 3 secretion system, forming oligomers and recruiting ASC, leading to the autoproteolytic activation of procaspase 1 and the cleavage of pro-IL-1 β into IL-1 β [47]. The missense mutations affecting the nucleotide-binding domain leads to higher constitutive and inducible levels of IL-1 β and IL-18, partly due to spontaneous (HEK cells) and ligand-induced (LPS-primed, flagellin-stimulated macrophage derived cells) formation of ASC multimers [44,45,46••]. The three GOF missense *NLRC4* alleles identified may act by a mechanism similar to that for GOF missense CAPS mutations (see above). Treatments targeting IL-1 may also be effective [44].

Blau syndrome (OMIM#186580) is characterized by granulomatous uveitis, joint inflammation, and skin inflammation [48] (Table 1, Figure 1). In 2001, mutations of *NOD2* (CARD15) were reported in four families [49••]. The same mutations were later found in

patients with early onset sarcoidosis — a sporadic disease with the same phenotype [50]. It has since become clear that this disorder can affect many other organs [51]. NOD2, a cytoplasmic protein, contains two CARDs, a NOD and a leucine-rich repeat domain and is produced mostly in myeloid cells, keratinocytes, intestinal, lung, and oral epithelia. Following binding of the bacterial muramyl dipeptide to the NOD domain, NOD2 forms a ‘nodosome’ with RIPK2, leading to activation of the NF- κ B and AP-1 signaling pathways and the subsequent induction of pro-inflammatory cytokines [52]. All the known disease-causing mutations affect the NOD domain. In 2005, the overexpression of the morbid alleles was shown to increase NF- κ B activation [53–55]. The constitutive localization of NOD2 mutants at the plasma membrane has also been observed in overexpression systems [55]. The GOF nature of these mutant alleles was firmly established by the excessively strong response of transfected HEK cells to muramyl dipeptide, contrasting strongly with the effect of the LOF alleles (from patients with Crohn's disease) used as negative controls [53]. The fine molecular and cellular mechanisms by which GOF mutations of *NOD2* cause the specific auto-inflammatory manifestations seen in Blau syndrome remain largely unknown.

Atypical hemolytic uremic syndrome (aHUS) (OMIM#235400) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure [56]. AR and AD aHUS can be caused by LOF mutations in genes encoding certain negative regulators of the complement pathway: *CFH*, *MCP*, *CFI*, *THBD*, and *CFHR1*. However, AD aHUS was recently shown to occur in patients bearing GOF mutant alleles of the *C3* [57••] and *CFB* [58••] complement activator genes. Both C3 and complement factor B (CFB) are produced by the liver. The three known complement pathways are activated by a sequential cascade of factors, eventually leading to the elimination of microorganisms, cell debris, and dead cells (for review [59,60]). They are tightly regulated by inhibitory factors. CFB upregulates the alternative pathway. Other factors downregulate the alternative pathway; these factors include MCP (or CD46), CD55, CFH, and CFI, LOF alleles of which may cause aHUS). The aHUS-causing variants, either by conferring a GOF on activators or a LOF on regulators, lead to faster or more sustained C3/CFB complex formation [57••,58••,61,62], resulting in constitutive activation of the C3/CFB complex (also called C3bBb). The aHUS-causing C3 and CFB variants are GOF, because the complex is hyperactive, whereas, biallelic LOF mutations of either of these genes in other patients inactivate or destabilize the complex, leading to susceptibility to infection, rather than aHUS [63,64].

Psoriasis (OMIM#177900) is a systemic inflammatory disorder with a strong, primary skin tropism, affecting about 2% of individuals of European descent. Monogenic forms of psoriasis are increasingly being recognized [65]. Recent studies have reported *CARD14* (*CARMA2*) mutations in patients with severe psoriasis [66,67••]. *CARD14* encodes a ubiquitously expressed protein with CARD and coiled-coil domains that can interact with the scaffold proteins BCL10 and MALT. Little is known about the function of *CARD14*, but its overexpression leads to NF- κ B activation [68]. All the GOF mutations identified affect the coiled-coil domain and increase NF- κ B activity in transfected HEK cells [66]. The analogy with *CARD11* (*CARMA1*), a *CARD14* paralog, for which some mutations have been shown to be GOF (see below), provides support for the notion that the *CARD14* mutations underlying psoriasis are GOF. This GOF leads to increases in the levels of

CCL20, IL-8, SOD2 and IL-36- γ in unstimulated keratinocytes [66], consistent with the reported discovery of psoriasis patients with mutations of the keratinocytic IL-1 antagonist gene *IL36RN* [65]. *CARD14* is ubiquitously and constitutively expressed, but the clinical phenotype associated with mutations is restricted to the skin. Further investigations of patients bearing *CARD14* GOF alleles should provide new insight into the mechanisms of psoriasis, potentially of broader value than just for the fraction of patients with *CARD14* mutations.

Autoinflammation with autoimmunity but without allergy or infection

The diseases hereafter described are among a group of recently characterized ‘interferonopathies’, which are characterized by a hyperactivity of type I interferons [69]. Our knowledge of the clinical spectrum and molecular basis of these syndromes has rapidly expanded in recent years.

Aicardi-Goutieres syndrome (AGS) (OMIM#225750) is the prototype type I interferonopathy, combining marked autoinflammation of the brain and meninges, and systemic signs of autoimmunity mimicking some of the features of systemic lupus erythematosus (SLE) [69,70]. It is an encephalopathy characterized, in its most severe form, by cerebral atrophy, leukodystrophy, intracranial calcifications, chronic cerebrospinal fluid lymphocytosis, and high levels of IFN- α in the cerebrospinal fluid. In 2014, GOF mutations of *IFIH1* were identified as the fifth genetic etiology of AGS [71]. *IFIH1* (also known as *MDA5*) encodes a cytosolic receptor for viral dsRNA intermediates [72•,73,74]. *MDA5* is activated by dsRNA and signals through the adaptor MAVS, which in turn activates IRF3 and NF- κ B via TBK1 and IKKs, leading to the induction of antiviral type I IFNs. All the *MDA5* mutations affecting the helicase domain are GOF, because they lead to an over-induction of type I IFN genes *in vitro* in an overexpression system, following induction by transfection with polyI:C [71]. *In vitro* studies have confirmed the tighter binding of RNA to *MDA5* and greater *MDA5* oligomer stability around the dsRNA [71,75], possibly accounting for the GOF. *MDA5* GOF heterozygous mice also develop autoimmunity (lupuslike nephritis, anti-nuclear factor and anti-dsDNA antibodies, deposition of immunoglobulin and complement in the kidney) [76], whereas knockout mice do not [77]. Despite the constitutive and ubiquitous expression of *IFIH1*, the clinical phenotype is almost completely restricted to the brain. Only one patient has been shown to have urticarial lesions, and none had infections. However, systemic autoimmunity was documented in three of the eight patients (autoantibodies against nuclear factor (3/8) and dsDNA (2/8)). Consistently, AGS and SLE can be allelic at other loci, including *TREX* in particular [78].

STING-associated vasculopathy, infantile-onset (SAVI) (OMIM#612374) combines systemic inflammation with peripheral vasculopathy and pulmonary lesions. Mutations of *TMEM173*, better known as *STING*, have been found in SAVI [79,80,81•]. *STING* is a cytoplasmic DNA sensor preferentially expressed in leukocytes. In the presence of dinucleotide (cGAMP), *STING* associates with IRF3 and TBK1, leading to the activation of type I IFN [82,83]. Mutations affecting the dimerization domain stabilize *STING* homodimers. The mutations are GOF, because overexpression of the mutant alleles increases baseline IFN- β expression over that for WT or LOF alleles [79]. An exacerbation of the IFN-dependent

gene expression ‘signature’ is observed *ex vivo* in leukocytes. One of the consequences is an increase in the phosphorylation of STAT family members (STAT1, STAT3, STAT5, and STAT6). The vasculopathy may be due to the intrinsic inflammation of endothelial cells, or to autoimmunity, as autoantibodies against phospholipids have been detected in several patients [79]. It is intriguing that GOF mutations of *MDA5* and *STING*, encoding cytosolic sensors of viral dsRNA and DNA, respectively, underlie such different and tissue-specific autoinflammatory conditions as AGS and SAVI. In-depth molecular and cellular studies, in animal models or, perhaps, the more directly relevant use of human iPSC technology to derive various non-hematopoietic cell types, should provide further insight into the pathogenesis of these fascinating disorders [84,85].

Infection with or without autoinflammation, autoimmunity, and allergy

We find here two specific conditions caused by different types of GOF mutations in the same gene.

PLCG2-associated antibody deficiency and immune dysregulation (PLAID, APLAID) (OMIM#614468, 614878) defines a new disease characterized by recurrent sinopulmonary infections and variable immune dysfunction: firstly, *PLAID* patients have cold-induced urticaria (allergy), due to mast-cell degranulation upon exposure to cold, and autoimmunity (anti-nuclear Abs), whereas secondly, *APLAID* patients have systemic autoinflammation with arthralgia, eye inflammation, and enterocolitis. GOF mutations of *PLCG2* have been associated with both conditions [86,87••]. *PLCG2* encodes a phospholipase C γ 2 (PLC γ 2) with expression restricted to the myeloid and lymphoid lineages, mostly in monocytes and dendritic cells, and in B and NK lymphocytes. Upon receptor activation (FcR, BCR or TCR), PLC γ 2 is phosphorylated, leading to the catalysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-bisphosphate (IP3) and diacyl glycerol (DAG). The in-frame deletions seen in *PLAID* patients and the missense mutation identified as responsible for *APLAID* affect the cSH2 domain of PLC γ 2, a domain inhibiting the lipase activity of this molecule. All mutations are GOF, as they increase PLC γ 2 activity in transfected cells at steady state and in response to stimulation (activation with RAC or EGF, respectively) [86,87••]. However, recent studies have suggested that BCR signaling may be impaired in *PLAID* patients [88], whereas IP3 or p-ERK levels are high in the B cells and PBMCs of *APLAID* patients [87••]. Heterozygous mice obtained by ENU mutagenesis and carrying another GOF mutation of *Plcg2* display paw auto-inflammation and increases in IP3 levels upon BCR activation, as in *APLAID* [89,90], whereas knockout mice do not [91]. Interestingly, mice with the same mutation but crossed with mice with a different genetic background presented autoimmunity (auto-Ab) [89]. In humans, the heterogeneity of the clinical phenotype, with *PLAID* and *APLAID* not only allelic to the *PLCG2* locus, but also both apparently caused by GOF alleles, raises important questions about the molecular and cellular mechanisms of disease. Studies of larger numbers of patients are required to delineate *PLCG2* genotypes and associated phenotypes more clearly, and mechanistic studies are required to clarify the mechanisms leading to antibody deficiency and to autoinflammation, autoimmunity, and/or allergy.

Autoimmunity with infection or allergy and without autoinflammation

Two very different diseases are described hereafter, one resulting in autoimmunity affecting mostly three organs, the other being characterized by unregulated B-cell proliferation with autoimmunity and increased risk of malignancy.

Infantile-onset multisystem autoimmune disease (ADMIO) (OMIM#615952) is an autoimmune disorder characterized by insulin-dependent diabetes mellitus (with anti-islet autoantibodies), autoimmune enteropathy, and celiac disease (which has an allergic component, characterized by hypersensitivity to alimentary gluten). Germline heterozygous *STAT3* mutations underlie this disease [92,93••]. *STAT3* encodes a widely expressed transcription factor. Many cytokines (*e.g.* IL-6, IL-11, IL-27, IL-31, IL-10, IL-22, IFN- α/β , LIF, and TGF β) activate *STAT3* by tyrosine phosphorylation, mediated by JAK kinases constitutively bound to cytokine receptors, resulting in the dimerization of *STAT3* and its translocation to the nucleus, where it drives gene transcription [94]. The ADMIO-causing *STAT3* mutations affect conserved residues within the SH2, transactivation or DNA-binding domains, leading to an increase in *STAT3* activity by an undefined mechanism independent of *STAT3* phosphorylation status (see *STAT1* below). LOF germline mutations affecting the same domains of *STAT3* are associated with AD hyper-IgE syndrome, a PID characterized by various non-hematopoietic signs, high serum IgE levels, and recurrent *Staphylococcus* and *Candida* infections [95,96]. However, some patients with GOF *STAT3* mutations also seem to have mild respiratory tract infections associated with hypogammaglobulinemia [93••]. The mechanisms underlying autoimmunity, allergy, and infection are unclear. Unlike patients with GOF *STAT1* mutations, who suffer principally from *Candida* and *Staphylococcus* infections, and from autoimmune thyroiditis (see below), patients with GOF *STAT3* mutations have a larger number of different autoimmune manifestations and fewer infections, with different microbes.

Hereditary polyclonal B-cell lymphocytosis, splenomegaly, and lymphadenopathy (OMIM #606445) is a disease associated with abnormal B-cell proliferation that can lead to B-cell chronic lymphocytic leukemia (B-CLL) or autoimmunity (autoantibodies). Heterozygous mutations of *CARD11* (also known as *CARMA1*) have been also been reported in four patients from two different families [97••,98]. *CARD11* encodes a cytoplasmic protein produced mostly in lymphoid cells. *CARD11* interacts with the scaffold protein BCL10 and MALT1 to form the 'BCM' complex, which activates NF- κ B. The activator of *CARD14* remains unknown, whereas *CARD11* mediates signaling by the activated BCR or TCR [68]. The mutations identified to date affect the coiled-coil domain. The two GOF *CARD11* mutant proteins aggregate spontaneously and form active signaling clusters with BCL10 and MALT1 in B and T lymphocytes, leading to constitutive activation of the canonical, but not the alternative NF- κ B pathway [97••]. These mutations are GOF and contrast with the biallelic LOF mutations of *CARD11* which cause a SCID-like phenotype with no functional T cells [99,100]. A somatic GOF mutation also leading to constitutive NF- κ B activation has previously been reported in diffuse large B-cell lymphoma [101]. Patients with GOF mutations have a B-lymphoproliferative disorder (with or without the production of autoantibodies) and recurrent infections (partly due to poor response to glycans). Interestingly, a lack of *CARD11* preferentially impairs the proliferation of T and B cells

(although B-cell and T-cell counts are in the normal range), whereas enhanced CARD11 activity drives uncontrolled B-cell proliferation.

Infection with or without autoimmunity and without autoinflammation or allergy

The genetic conditions hereafter described may be associated with a wide spectrum of infection and autoimmunity. Anhidrotic ectodermal dysplasia and immunodeficiency (EDA-ID) is the prototypic inborn error of NF- κ B-dependent immunity, accounting for its pleiotropic manifestations. Other conditions include susceptibility to papillomaviruses as well as bacterial or atypical mycobacterial infections and malignancies in the Warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome, or *Candida albicans* infection and thyroid autoimmunity in AD chronic mucocutaneous candidiasis (CMC). Finally, in activated *PI3K- δ* syndrome (APDS) and GOF mutations of *PIK3R1*, two disorders of the PI3 kinase pathway, chronic sinopulmonary infection is the prominent manifestation, similarly to many B-cells or partial T and B cells deficiencies.

Anhidrotic ectodermal dysplasia and immunodeficiency (EDA-ID) (OMIM#612132) is characterized by ectodermal dysplasia with several defects of innate and adaptive immunity, underlying various infections. A GOF mutation of *NFKBIA* found in a single patient was reported in 2003 [8•] to mimic LOF (hypomorphic) mutations of *NEMO* [102], illustrating the power of genetic studies on single patients [103]. Other patients have since been described [104–108]. *NFKBIA* encodes I κ B α , an inhibitory protein that binds NF- κ B dimers and retains them in the cytoplasm. Upon stimulation (*e.g.* by TNF- α , IL-1 β , or TLR agonists, BCR and TCR activation), the IKK complex phosphorylates the Ser32 and Ser36 residues of I κ B α , leading to a change in conformation and the degradation of I κ B α , unmasking the NLS of NF- κ B, leading to its translocation to the nucleus. GOF mutations are missense for those affecting Ser32 or Ser36, or N-terminal nonsense mutations facilitating the re-initiation of translation after the two serine residues. The mutant I κ B α proteins lack one or both serine residues, and therefore gain inhibitory activity. These hypermorphic proteins stably bind NF- κ B, do not dissociate normally from it, and cannot be targeted to the proteasome [104–106]. These hypermorphic GOF alleles of *NFKBIA* mimic hypomorphic LOF alleles of the X-linked *NEMO/IKBKG* genes. The T-cell phenotype appears to be more pronounced in patients with GOF alleles of *NFKBIA* [102,109]. EDA-ID patients with GOF I κ B α mutations have a combination of myeloid and lymphoid immunodeficiency and extra-hematopoietic manifestations, reflecting the breadth of NF- κ B physiology. Hematopoietic stem cell transplantation has been shown to be successful in only one patient to date [106,107,110,111]. One patient with systemic autoinflammation has been described [107]. Allergy and autoimmunity have not been reported in these patients. However, autoimmunity would be expected to occur, given the profound T-cell phenotype. The various infections can be attributed to defects of specific receptors upstream from I κ B α and NF- κ B, as the corresponding mutations have been described in other patients. For example, invasive pneumococcal and staphylococcal diseases result largely from impaired TLR and IL-1R signaling, as suggested by the phenotype of IRAK-4-deficient and MyD88-deficient patients [112–116]. The description of mutations in other genes will progressively

clarify the pathogenesis of other infectious and immunological phenotypes affecting EDA-ID patients.

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) (OMIM#193670) is caused by mutations of *CXCR4* [117-119]. This gene encodes a G protein-coupled seven-transmembrane segment receptor (a member of the rhodopsin family) that is broadly expressed in leukocytes and other cells. This receptor is activated by secreted SDF-1 (CXCL12, almost ubiquitous but absent from blood cells), and it then undergoes a change in conformation, activating signaling *via* the heterotrimeric Gαβ-γ-protein complex. Concomitantly, phosphorylation of the serine residue at the C-terminus of *CXCR4* allows the binding of β-arrestins, triggering endocytosis of the receptor and its desensitization to ligand stimulation [120,121]. Surprisingly, most WHIM-causing mutations identified to date are premature C-terminal nonsense mutations, abolishing *CXCR4* phosphorylation and thereby increasing induced signal transduction by inhibiting recycling and desensitization [117,122-124]. The broad expression pattern of *CXCR4* is consistent with the broad clinical phenotype of WHIM, most features of which remained unexplained at the cellular level. Some patients also develop malignancies (carcinoma, EBV-driven B and T cell lymphoma) [125]. Consistent with the GOF nature of WHIM-causing mutations, *CXCR4* inhibitors were recently shown to reverse myelokathexis in a mouse xenotransplantation model [126]; these inhibitors are currently being tested in humans [127]. The mechanisms underlying low memory B-cell counts and warts (caused by alpha-HPV, by contrast to epidermodysplasia verruciformis (EV), in which EV-defining warts are caused by beta-HPV) [128] remain unknown.

Chronic mucocutaneous candidiasis (CMC) (OMIM#114580) is characterized by recurrent or persistent peripheral infections caused by the fungus *C. albicans*. Mutations of *STAT1* were first reported in patients with AD CMC in 2011 [129-131] and have since been found in about half the patients with this condition [132-150]. These patients also suffer from a few other infectious diseases, such as staphylococcal disease, and autoimmunity is also prominent, as half these patients have autoimmune thyroiditis [141,143,150]. Mucocutaneous carcinomas can also develop [130,151]. *STAT1* encodes a transcription factor with a coiled-coil domain and a DNA-binding domain that is expressed principally in hematopoietic cells, lymph nodes, and smooth muscle. *STAT1* can be activated *via* JAKs, following binding to various cytokines (IFNα/β/λ, IFNγ IL-27, IL-6, and IL-21), by general mechanisms similar to those described above for *STAT3*. In patients, mutations affecting the coiled-coil and DNA-binding domains lead to an excess of p-*STAT1*-driven target gene transcription. The GOF results from impairment of the nuclear dephosphorylation of p-*STAT1* [129]. Interestingly, human *STAT1* LOF results in lower levels or an absence of phosphorylation and is associated with MSMD and viral infection (an AR form impairing IFN-α/β, IFN-γ, IFN-λ and IL-27 responses) [152] or MSMD (an AD form impairing only the IFN-γ response, by negative dominance) [153]. *STAT1* GOF mutations impair the development of IL-17 T cells, accounting for the CMC observed in affected patients, as mutations of the *IL17F*, *IL17RA* and *ACT1* genes have been shown to cause CMC [154,155]. They also underlie autoimmunity, including thyroiditis in particular, probably due to the enhancement of IFN-α/β signaling [156].

Activated PI3K- δ syndrome (APDS) (OMIM#602839) is characterized by recurrent sinopulmonary infections and combined T-cell and B-cell immunodeficiency. A mutation of *PIK3CD* (E1021K) was first reported in 2006, in one patient [157•]. Additional kindreds with *PIK3CD* mutations were discovered later. This, together with the elucidation of the molecular mechanism of disease, made it possible to determine the pathogenic role of these mutations [158–162]. *PIK3CD* encodes the phosphatidylinositol-3-Kinase subunit p110 δ , which is expressed only in progenitor and derived hematopoietic cells. The p110 δ subunit is a catalytic subunit that, together with a regulatory subunit (p85 α , p55 α , p55 β or p85 β) forms a heterodimeric lipid kinase that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to give phosphatidylinositol 3,4,5-trisphosphate (PIP3) [163]. Upon activation by growth factor and cytokine, p110 δ generates PIP3, which, in turn, activates AKT (p-AKT), PDK1, and mTOR. All APDS-causing mutations enhance activity, leading to the production of more PIP3 and increasing p-AKT levels *in vitro* in both basal conditions and upon TCR stimulation. Like a somatic GOF p110 δ mutation previously identified in cancer cells [164], the germline mutations may be GOF because of the enhanced association of p110 δ with membranes, increasing the levels of both steady-state and inducible activity. These germline GOF alleles underlie a broad clinical phenotype, with chronic B lymphoproliferation, chronic viral replication, and recurrent bacterial infections. They seem to decrease the amounts and affinity of antigen-specific antibodies (Ab), with low levels of antibodies against the bacterial capsule in particular. This Ab deficiency is probably a consequence of B-cell lymphopenia, with small numbers of memory B cells in particular. These patients have also diminished counts of naive T cells, with an over-representation of senescent effector T cells.

GOF mutations of PIK3R1 (OMIM#616005) cause a related disorder also characterized by recurrent sinopulmonary infections and immunodeficiency [165]. The molecular mechanism of disease was characterized in more depth in a more recent study [166••]. *PIK3R1* encodes p85 α , p55 α and p50 α , the regulatory subunits of p110 δ [163]. Mutations of the splicing site of exon 10 lead to the generation of a novel splice variant without exon 10, encoding a new product lacking amino acids 434–475 of p85 α (near the SH2 domain). Higher steady-state levels of p-AKT are observed *in vitro* and *ex vivo*, indicating that the mutations are GOF. Thus, GOF mutations of *PIK3R1* and *PIK3CD* seem to underlie immunological and clinical phenocopies [160,161]. *PIK3R1* is more broadly expressed than *PIK3CD*. However, the clinical phenotype associated with these mutations seems to be mostly restricted to the consequences of a leukocyte defect, with only recurrent infections and antibody deficiency. Lymphoproliferation and autoimmunity have however also been reported [165,166••] but there were no overt signs of autoinflammation or allergy. Interestingly, other heterozygous *PIK3R1* mutations have been reported in SHORT syndrome (OMIM#269880), without immunodeficiency, and these mutations appeared to decrease p-AKT levels in response to insulin [167–171]. Moreover, a homozygous LOF mutation of *PIK3R1* had previously been shown to cause agammaglobulinemia and a selective blockade of B-cell development [172]. It is interesting that too little (AR deficiency) and too much (AD by GOF) *PIK3R1* cause different forms of B-cell deficiency.

Conclusion

AD GOF PIDs are more frequent than was initially thought. Since 2003, when a missense I κ B α mutation was convincingly demonstrated to be GOF in a single patient [8•,103], 17 AD inborn errors causing a GOF have been reported and diagnosed in several thousand patients (Table 1, Figure 1). These GOF mutations are striking in terms of their genetic, immunological, and clinical diversity. In the future, a number of known and new conditions, manifesting as various sporadic or familial, mild or severe phenotypes, infectious, autoimmune, autoinflammatory, tumoral, and/or allergic diseases, will probably be attributed to novel AD GOF PIDs. Next-generation sequencing in the form of whole-exome and whole-genome sequencing, will undoubtedly lead to an avalanche of discoveries of such defects [6]. It will be particularly interesting if GOF mutations of genes for which LOF mutations have already been associated with AD disease can be found, such as those already known in *STAT1* and *STAT3*. LOF and GOF mutant alleles underlying AD disorders at the same locus may be seen as insightful experiments of Nature, shedding new light on the quantitative regulation of immunity, a question not commonly studied in inbred mice. As discussed in this review, knock-in mice have been instrumental in modeling AD GOF PIDs, just as they have been for AD LOF PIDs, whether by haploinsufficiency (*e.g.* CHD7, [173]) or by negative dominance (*e.g.* STAT3 [174]). In the four cases investigated to date, mice heterozygous for GOF alleles reproduced some features of the human phenotype [29,30,42,76,89,90]. The same apparently applies to AD PIDs based on negative dominance. However, it seems to be less often the case for haploinsufficiency, as illustrated by the lack of autoimmunity in *Ctla4*^{+/-} mice, at odds with the findings for heterozygous patients [175,176]. The results obtained seem to be more consistent between mice and humans for gains of activity than for haploinsufficiency. The study of human GOF mutations underlying inborn errors of immunity will pave the way for the search for gene duplications (or larger lesions), which might exert a gene dosage effect, mirroring that of haploinsufficiency. Whether mono-allelic or biallelic, a deletion of an entire gene is by definition LOF (but not necessarily dominant), whereas a duplication of an entire gene is not necessarily GOF (as its expression may be regulated). AD PIDs by this novel type of GOF may soon be discovered, as suggested (but not demonstrated yet) by the *de novo* duplication of a large region encompassing *TNFRSF11A* (encoding protein RANK, which is expressed in blood mononuclear cells), which was recently found in a single patient with early-onset recurrent fever [177]. Such progress would potentially shed light on the pathogenesis of a number of chromosomal disorders, including Down's syndrome in particular, the immunodeficiency of which has remained of elusive pathogenesis [178,179].

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Highlights

- Gain-of-function mutations can cause autosomal dominant inborn errors of immunity.
- These disorders are increasingly recognized and often due to *de novo* germline mutations.
- They underlie various combinations of infection, cancer, allergy, autoimmunity, or autoinflammation.

Figure 1.

Clinical manifestation of 17 AD GOF PIDs. Infections are defined as conditions caused by infectious agents: viruses, bacteria, fungi or parasites. Allergies are defined as conditions caused by hyperreactivity to environmental triggers, including, in particular, but not exclusively, T-cell and/or B-cell antigens. Autoimmunity is defined as disease caused by self antigen-reactive T cells and/or B cells. Malignancy is defined by the uncontrolled proliferation of cells, such as leukemia or lymphoma. Other clinical diseases with immunological mechanisms are collectively referred to as autoinflammation, comprising at least the six categories proposed by Dan Kastner [180], and including a growing number of syndromes and conditions. We arbitrarily excluded inborn errors of osteoclasts from this classification (see section ‘Introduction’). Each of these five categories is highly diverse clinically and immunologically. Several AD PIDs by GOF display features from two or more of these four broad types of manifestations. We do not use the term ‘immune dysregulation’, for which no precise definition is available. We also refrain from using the term ‘immunodeficiency’, which may be ambiguous (more than the term PID, the broad signification of which is now widely accepted), referring sometimes, but not always, to an immunological deficit underlying infections and excluding autoimmunity, autoinflammation, allergy, and malignancy.

Table 1

Autosomal dominant inborn errors of immunity involving a gain of function

Gene (product)	Condition/ acronym	Clinical phenotype	Immunological phenotype	Auto inflammation	Auto immunity	Infection	Allergy	Malignancy	Genotype	Proven GOF	Mouse model	Penetrance	De novo	References
<i>NLRP3</i>	CAPS (FCAS, MWS, CINCA/ NOMID)	Cryopyrin-associated periodic syndromes; from cold-induced rash, arthralgia, fever and conjunctivitis to chronic, aseptic, neutrophilic meningitis, earing loss and, in some cases, cartilage bone hypertrophy	Myeloid cells — increased IL- β	+	—	—	—	—	2001	2012	2009-K1-Hz[29,30]	Incomplete High	Yes	[18••,19]
<i>PSTPIP1</i>	PAPA syndrome	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne	Myeloid cells — increased IL- β	+	—	—	—	—	2002	2007	2013-Ectopic-Hz[42]	Complete	Yes	[37••]
<i>NLR4</i>	HLH	Early-onset autoinflammatory syndrome and macrophage activation syndrome	Ubiquitous — increased IL- β	+	—	—	—	—	2014	2014	No	Complete	Yes	[44,45]
<i>CARD15</i> (NOD2)	BLAU syndrome	Granulomatous uveitis, joint inflammation and skin inflammation.	Myeloid cells, keratinocytes, intestinal lung and oral epithelia — increased NF- κ B activation	+	—	—	—	—	2001	2005/14\$	No	Incomplete High	Yes	[49••]
<i>CFB</i> *	aHUS	Atypical hemolytic and uremic syndrome	Liver — increased complement activation	+	—	—	—	—	2007	2007	No	Incomplete	Yes	[58••]
<i>C3</i> *	aHUS	Atypical hemolytic and uremic syndrome	Liver — increased complement activation	+	—	—	—	—	2008	2008	No	Incomplete	nr [†]	[57••]
<i>CARD14</i>		Psoriasis and related conditions	Ubiquitous — increased NF- κ B activation	+	—	—	—	—	2012	2012	No	Incomplete High	Yes	[66]
<i>IFIH1</i> (MDA5)	AGS	Atcadi-Goutieres syndrome (aseptic meningitis, encephalopathy, brain calcinosis)	Ubiquitous — increased type I interferon	+	+/-	—	—	—	2014	2014	2014-ENU-Hz [76]	Incomplete High	Yes	[71]
<i>TMEM173</i> (STING)	SAVI	Early onset inflammation with peripheral vasculopathy and lung involvement (STING-associated vasculopathy with onset in infancy)	Leukocytes — increased type I interferon	+	+	—	—	—	2014	2014	No	Complete	Yes	[79]
<i>PLCG2</i>	PLAID	Infections, autoimmunity, cold urticaria	Monocytes, B cells and NK- cells — increased IP3 and DAG	—	+	+	+	—	2012	2012	2005-K1-Hz [89,90]	Complete	Yes	[86,87••]

Gene (product)	Condition/ acronym	Clinical phenotype	Immunological phenotype	Auto inflammation	Auto immunity	Infection	Allergy	Malignancy	Genotype	Proven GOF	Mouse model	Penetrance	De novo	References
STAT3 [#]	APLAID	Infections, autoinflammation		+	–	+	–							
		Early-onset autoimmune disease	Lymphoid cells — constitutive activation of STAT3	–	+	+	+	–	2014	2014	No	Complete	Yes	[92]
CARD11 [*]		B lymphocytosis	Lymphoid cells — constitutive NF-κB activation	–	+	+/–	–	+/–	2012	2012	No	Complete	nr ^{**}	[97••]
NFKB1A (IkBa)	EDA-ID	Anhidrotic ectodermal dysplasia with immunodeficiency	Ubiquitous — impaired NF-κB- dependent immunity	–	–	+	–	–	2003	2003	No	Complete	Yes	[8••].
CXCR4	WHIM	Warts, hypogammaglobulinemia, infections and myelokathexis	Bone marrow, granulocytes, B cells — constitutive activation of CXCR4 pathway	–	–	+	–	+/-	2003	2003/2005§	2007-Xenograft	Complete	Yes	[117••]
STAT1 ^{*#}	CMCD	Chronic mucocutaneous candidiasis, auto-immune thyroiditis	Lymphoid cells — low IL-17 — constitutive activation of STAT1	–	–/+	+	–	+/-	2011	2011	No	Complete	Yes	[129,130••]
PIK3CD (p110δ)		Multiple bacterial and viral infection — autoimmunity	T and B cells - increased PIP3	–	–/+	+		+/-	2006	2013	No	Complete	Yes	[157•\158••]
PIK3R1 [*]		Recurrent bacterial infection	B-cells — increased p-AKT	–	–	+	–	–	2014	2014	No	Complete	Yes	[165]

KI: knock-in, Hz: heterozygous, nr: not reported.

^{*} There is also an AR disorder due to LOF alleles.

[#] There is also an AD disorder due to LOF alleles.

^{**} Too few kindreds to draw firm conclusions.

[§] Suggestion of GOF/firm conclusion of GOF.