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IL12Rβ1: The cytokine receptor that we used to know

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Abstract

Human *IL12RB1* encodes IL12Rβ1, a type I transmembrane receptor that is an essential component of the IL12- and IL23-signaling complex. *IL12RB1* is well-established as being a promoter of delayed type hypersensitivity (DTH), the immunological reaction that limits tuberculosis. However, recent data demonstrate that in addition to promoting DTH, *IL12RB1* also promotes autoimmunity. The contradictory roles of *IL12RB1* in human health raises the question, what are the factors governing *IL12RB1* function in a given individual, and how is inter-individual variability in*IL12RB1* function introduced? Here we review recent data that demonstrate individual variability in *IL12RB1* function is introduced at the epigenetic, genomic polymorphism, and mRNA splicing levels. Where and how these differences contribute to disease susceptibility and outcome are also reviewed. Collectively, recent data support a model wherein*IL12RB1* sequence variability – whether introduced at the genomic or post-transcriptional level - contributes to disease, and that human *IL12RB1* is not as simple agene as we once believed.

INTRODUCTION

Interleukin-12 and interleukin-23 (IL12/23) are proinflammatory cytokines that contribute to multiple aspects of human immunity. Far from being restricted to humans, the proinflammatory properties of IL12/IL23 have been conserved throughout evolution, as phylogenetically diverse vertebrates express IL12/IL23 in response to their natural pathogens (1–16) (Fig 1A). Among human bacterial pathogens, the modulation of IL12/IL23 expression is largely associated with species' Gram staining characteristics (17–61) (Fig 1B). The activities of IL12/IL23 are dependent on IL12Rβ1, a type 1 transmembrane receptor that physically associates with the p40-domain common to both IL12/IL23 and promotes their respective signaling pathways (62). Encoded by the gene *IL12RB1*, IL12Rβ1 physically associatesIL12 and IL23 and signals in complex with IL12Rβ2 or IL23R, respectively (63–65) (Fig 2). The extracellular portion of IL12Rβ1 contains the cytokine-binding region essential for physical association with IL12/IL23, whereas the cytoplasmic portion acts in concert with IL-12Rβ2/IL-23R to transmit intracellular signals via the pre-

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associated kinases TYK2 and JAK2 (66). Solidifying *IL12RB1*'s association with protective immune responses, individuals who are homozygous for *IL12RB1*^{null} alleles are susceptible to persistent forms of several diseases, including tuberculosis, salmonellosis and candidiasis (67, 68).

In this article, we review recently published data that have variegated our model of*IL12RB1* biology and function. We first revisit the early data that underlie immunologists' basic understanding of*IL12RB1* and its function as a promoter of delayed type hypersensitivity (DTH, the inflammatory response most associated with intracellular pathogen clearance). These early data are contextually important for recognizing the significance of more recent advances, among which are demonstrations that *IL12RB1* promotes human autoimmunity in addition to DTH, and that inter-individual variability in human*IL12RB1* activity is introduced at the epigenetic, genomic, and mRNA-splicing levels. How inter-individual variability is either known or hypothesized to affect disease susceptibility will also be discussed. Finally, we will also review the recent discovery of multiple novel IL12p40-heterodimers, which suggests *IL12RB1* is involved in additional signaling pathways that have yet to be discovered. Collectively, the data we review demonstrate that our understanding of *IL12RB1* is far from complete, and that IL12Rβ1 not as simple a receptor as we once thought.

First impressions: The discovery of IL12Rβ1

Although many immunologically-significant proteins are first discovered in model organisms with primitive immune systems (e.g. fruit flies, zebrafish, mice), the discoveries of IL12 and IL12Rβ1 are notable exceptions, having both been initially isolated using human tissues (65, 69, 70). IL12 was discovered at the Wistar Institute by Kobayashi et al. (69), who purified the cytokine from the supernatants of human B-lymphoblasts as "natural killer cell stimulating factor"; an engaging recollection of this discovery was published several years ago (71). At Hoffman-La Roche (Nutley, NJ), Stern et al. independently purified IL12 from B-lymphoblast supernatants as "cytotoxic lymphocyte maturation factor" (70). The discovery of IL12 precipitated a series of studies at Hoffman-La Rocheto identify the receptor responsible for IL12's bioactivity. These studies, which led to the cloning and characterization of human IL12Rβ1, are an impressive tour de force of immunology and biochemistry even by today's standards (64–66, 72–74).

To clone the human IL12 receptor, a team led by Ueli Gubler used the monoclonal antibody 2-4E6 (which immunoprecipitates an IL12-binding surface complex from activated PBMCs) to pan COS-cells transfected with a PBMC cDNA library, isolating those cells that bound both 2-4E6 and IL12 (65). This screen identified a single cDNA clone (clone 5), which encoded the protein we now refer to as IL12Rβ1. Based on its homology to gp130, IL12Rβ1 was predicted to be a type 1 transmembrane protein (65). IL12Rβ1's affinity for IL12 (K_d=3 nM) supported a model wherein IL12Rβ1 contributed to IL12 bioactivity; cross-linking studies not only confirmed the physical interaction between IL12 and IL12Rβ1, but also demonstrated that oligomers of IL12Rβ1 – not monomers – underlie this 3 nM affinity (IL12Rβ1 monomers bound IL12 with a $K_d \geq 50$ nM). However, the fact that PHA-activated human T lymphoblasts have three classes of IL12-binding sites (high affinity, K_d=5–20 pM;

intermediate affinity, K_d=50–200 pM; low affinity, K_d=2–6 nM) (72, 73) suggested that additional IL12 receptor components existed and had not yet been identified. A second component of the IL12 receptor complex, IL12Rβ2, was subsequently identified by Presky et al. (64) to bind IL12 with a low affinity when expressed alone (K_d= 5 nM); relative to IL12Rβ1, IL12Rβ2 contained a larger cytoplasmic domain that promoted intracellular signaling. WhenIL12Rβ1 and IL12Rβ2 were co-expressed, COS cells obtained both low-affinity (K_d=~7.5 nM) and high-affinity (K_d=~55 pM) IL12 binding sites (64); only when both IL12Rβ1 and IL12Rβ2 were expressed did Ba/F3 cells optimally proliferate in response to IL12, indicating that both were required for intracellular signal transduction (64). That IL12Rβ1 and IL12Rβ2 respectively associate with the p40- and p35-domains of IL12 (74), and each chain has different intracellular associating kinases (66), led to the "textbook model" of IL12 signaling that is now immunology canon (Fig 2A–B).

The notion that IL12Rβ1 is essential for resistance to intracellular bacterial pathogens stems from the characterization of IL12Rβ1-knockout mice (75) and identification of *IL12RB1*-deficient individuals (76, 77). After cloning and characterizing human IL12Rβ1, Ueli Gubler led efforts to clone IL12Rβ1's mouse homologvia cross-hybridization with mouse ConA-lymphoblast RNA(78); this eventually led to the generation of IL12Rβ1-knockout (*il12rb1*$^{-/-}$) mice by Jeannie Magram, who was also then at Hoffman-La Roche (75). At homeostasis, *il12rb1*$^{-/-}$ mice were nearly identical to wild type controls in viability, fertility, and CD4:CD8 T cell ratio. However, upon activation and exposure to IL12, T_H cells from *il12rb1*$^{-/-}$ mice exhibited defective production of IFNγ – a cytokine known at the time to be critical for delayed type hypersensitivity (DTH) (79, 80). Around the same time *il12rb1*$^{-/-}$ mice were being characterized, the laboratories of Jean Laurent Casanova (then at INSERM in Paris, France) and Tom Ottenhoff (Leiden University in Leiden, Netherlands) identified *IL12RB1*-deficient individuals in several Mediterranean communities[20,21]. While for the majority of their lives*IL12RB1*-deficient individuals were asymptomatic (81), the same individuals developed disseminated and recurrent diseases following exposure to mycobacterial and salmonella pathogens (68). Similar to *il12rb1*$^{-/-}$ mice, T_H cells from *IL12RB1*-deficient individuals also exhibited defective production of IFNγ[20,21]. Since the initial reports of Casanova and Ottenhoff, > 30 studies across multiple ethnicities have solidified *IL12RB1*'s reputation as being essential for resistance to several intracellular pathogens, including those of bacterial, fungal, tuberculous and non-tuberculous mycobacterial origin (68).

First impressions aren't everything:*IL12RB1* as a contributor to autoimmunity

Complicating *IL12RB1*'s reputation as a promoter human health is its association with IL23 signaling, which positively regulates inflammation in numerous animal models of autoimmunity (82) (Fig 2C–D). Whereas IL12 is a heterodimer of IL12p35 (encoded by *IL12A*) and IL12p40 (encoded by *IL12B*), IL23 is a heterodimer of IL12p40 and a 19 kDa protein (p19) encoded by *IL23A*. IL23 was discovered by using a combination of computational and overexpression approaches (63, 83); it contributes to animal models of autoimmunity via its promotion of pathogenic T_H17 cells (82), a feature first observed in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS) (84). The fact that IL23 contained an IL12p40-domain strongly suggested that IL12Rβ1 was

involved in IL23-signaling. Although IL12Rβ1's interactions with IL23 are not as well-characterized as those between IL12Rβ1 and IL12 (e.g. no affinity measurements have ever been reported), its involvement in IL23-signaling is supported by the fact that IL23 binds the surface of IL12Rβ1-transfected Ba/F3 cells (63). Conversely, IL23 is unable to bind or elicit STAT4-phosphorylation in *IL12RB1*-deficient human leukocytes (both binding and STAT4-phosphorylation are rescued following retroviral-transduction of *IL12RB1*-deficient leukocytes with the IL12Rβ1 cDNA) (85); $CD4^+$ T_H cells from *il12rb1*$^{-/-}$ mice and *IL12RB1*-deficient individuals are also resistant to IL23-dependent T_H17-differentiation (85, 86).

Importantly, the establishment of IL23 as being a promoter of T_H17-driven autoimmunity should not preclude consideration of IL12 in autoimmune disease models, as IL12 drives the differentiation of T_H1 cells that are capable of transferring experimental autoimmune uveoretinitis (EAU, the animal model of human uveitis) (87), and T_H1 cells drive hepatocellular damage in a model of fulminant autoimmune hepatitis (88). Likewise, pathogen control is not solely the purview of IL12, as IL23 is essential for limiting fungal burden in animal models of oropharyngeal candidiasis (89) and *Pneumocystis carinii* infection (90). Given the biological similarities between IL12 and IL23 function (63, 91) and the number of pathogens that elicit IL12p40 expression (Fig 1), it is likely that IL12 and IL23 evolved to control different infections at different tissue sites, and that each contribute to pathology when their levels, duration of expression, or site of action are not properly regulated.

Despite the number of studies supporting mouseIL12/IL23's involvement in promoting mouse autoimmunity, humanIL12/IL23's involvement in promoting human autoimmunity was brought into question by the results of Segal al. (92), who reported that ustekinumab-treatment failed to reduce the number of cranial lesions in relapsing-remitting MS patients. Ustekinumab is a human monoclonal antibody specific to the IL12p40-chain common to both IL12 and IL23 (93); its ability to neutralize human IL12 bioactivity and prevent EAE had been demonstrated (94, 95). The results of Segal et al. not only cast doubt on IL12/IL23's role in human autoimmunity (96), but also the general utility of animals as models of human autoimmunity (97). However, recent data has reaffirmed the role of IL12/IL23 in other human autoimmune diseases, if not MS. Specifically, ustekinumab has been shown to be an effective treatment for plaque psoriasis, psoriatic arthritis and refractory Crohn's disease (98–100). Additional trials testing ustekinumab's efficacy as a treatment for additional autoimmune diseases are currently underway (https://clinicaltrials.gov).

Shades of grey: Variable *IL12RB1* function as introduced at the epigenetic, genomic, and mRNA-splicing level

The dual roles of IL12Rβ1 as promoter of both pathogen-resistance and autoimmunity raises the question: what are the factors that govern IL12Rβ1's sensitivity to IL12/IL23 in a given individual and, by extension, its ability to prevent or cause harm? As with many traits, an individual's sensitivity to IL12/IL23 is governed by multiple factors, including those that are heritable (e.g. the *Tpm1* locus (101)) and non-heritable (e.g. temperature (102), microbiome (103, 104) and age (105)). Here we will review the epigenetic, genomic, and mRNA-

splicing factors specific to *IL12RB1* that underlie individual differences in IL12/IL23 sensitivity and associate with disease susceptibility. Notably, although IL12Rβ1 functions similarly in mice and humans, important differences exist between the genomic organization and mRNA-splicing of mouse *il12rb1* (Fig 3) and human *IL12RB1* (Fig 4); these differences are highlighted.

IL12RB1 variation at the epigenetic level—Between otherwise genetically identical individuals, epigenetic differences arise that cause inter-individual variation in gene expression (106). Human *IL12RB1* is one such gene that epigenetically differs between individuals (107). *IL12RB1* is on chromosome 19, which is among the most gene dense chromosomes, and the most homologous to other animals (108); in *IL12RB1*'s immediate vicinity are other positive regulators of DTH, including Mast3 (109), and Jak3 (110), and Ifi30 (111). In mice, transcription of IL12Rβ1 is driven by a promoter region that begins 2.5kb upstream of the *il12rb1* start site (112). Elements of this promoter region are conserved in humans, including an interferon-stimulated response element (ISRE) and putative binding sites for the transcription factors PU.1, NFκB-, USF, GATA1 and STAT proteins. The promoter elements and transcription factors are responsible for IL12Rβ1 transcription are cell type-specific. In MΦs stimulated with IFNγ and IL15, IL12Rβ1 transcription is principally driven by PU.1, IRF3 (via association with the ISRE), and to a lesser extent, IRF1/2 and IRF7. However, since PU.1 expression is primarily restricted to B cells and MΦs (113), the mechanisms that regulate IL12Rβ1 transcription in T_H cells necessarily differ from those that regulate IL12Rβ1 transcription in MΦs. Namely, T_H1 cell transcription of IL12Rβ1 is principally driven by IRF1 and STAT4: the *il12rb1* promoter in T_H1 cells physically associates with both IRF1 (86) and STAT4 (114), and IL12Rβ1 expression is diminished in IRF1-deficient (86) and STAT4-deficient T_H1 cells (115). IRF3-deficiency, on the other hand, does not affect T_H1 IL12Rβ1 expression (86); deletion of the *IL12RB1* promoter PU.1 element from a luciferase reporter also did not affect *IL12RB1* transcription in Jurkat cells (a human T lymphoma cell line) (116). Consistent with T_H1 IL12Rβ1 expression being required for control of mycobacterial infection (117), IRF1- and STAT4-deficiency both confer susceptibility to mycobacterial infection (115, 118–120) while IRF3-deficiency does not (121). Curiously, in addition to IL12Rβ1 transcription being driven by distinct elements in MΦ/DCs and lymphocytes, activation of IL12Rβ1 in DCs leads to intracellular tyrosine-phosphorylation events that are distinct from those observed in lymphocytes. Specifically, Nagayama et al. (122) demonstrated that tyrosine-phosphorylated IL12Rβ1-associated proteins differ between IL12-stimulated DCs and lymphoblasts. These differences possibly contribute to the different transcriptional signatures of IL12-stimulated T_H cells (ERM, IRF1) (123, 124) versus IL12-stimulated DCs (IL1β, IL6, IL12p35, IL12p40 and MHCII) (122, 125). The results of Nagayama et al. (122) also suggest that the effects and therapeutic value of IL12Rβ1 activation or suppression will vary depending on the immune cell composition present in the tissue of interest.

In addition to promoting transcription of IL12Rβ1, IRF1 is also a key factor governing whether IL12Rβ1-dependent signals lead a naïve T_H cell to become a T_H1 cell or T_H17 cell (86). In the presence of IRF1, IL12Rβ1-driven signals bias a naïve T_H cell to become a T_H1 cell; in the absence of IRF1, IL12Rβ1-driven signals bias a naïve T_H cell to become a T_H17

cell (86). This observation is surprising given that diminished IL12Rβ1 transcription (as a consequence of IRF1-deficiency) would presumably impact upon both IL12- and IL23-signaling. The model proposed to explain this observation result is that lower levels of IL12Rβ1 expression are sufficient for IL23-signaling (and thus T_H17 differentiation), while greater levels are required for IL12-signaling (and thus T_H1 differentiation). Following their differentiation, human T_H1 and T_H17 cells express *IL12RB1* at equivalent levels (126).

Histone methylation is an epigenetic factor that regulates transcription factors' access to the IL12Rβ1 promoter (112). In T_H1 cells, the *il12rb1* gene is differentially methylated depending on the presence of STAT4 (114). Specifically, the extent to which *il12rb1* is methylated on histones H3K4 and H3K36 declines in the absence of STAT4; methylated H3K4 is primarily located near the transcriptional start site, while methylated H3K36 is located within the gene body (114). It can only be speculated at this time, but it is possible that differences in the extent to which *IL12RB1*-associated histones are modified influence individual disease susceptibility. Supporting this speculation are the results of Zawada et al. (107), who recently reported that *IL12RB1* is more methylated in peripheral leukocytes of individuals with uremia-associated atherosclerosis. Whether *IL12RB1* methylation is a cause or consequence of uremia-associated atherosclerosis is difficult to determine, but the results of Cohen et al. (127) demonstrate that once methylation patterns of differentiated human T_H1/T_H17 are established, they are not easily changed.

IL12RB1 variation at the genomic level—While *IL12RB1* is not a mutational hot spot per se (128), it exhibits a high degree of polymorphism that associates with susceptibility to number of diseases (129). Here we review nine single nucleotide polymorphisms (SNPs) that influence disease and are common depending on an individual's ethnicity (Fig 4A–B): rs393548, rs436857, rs372889, rs383483, rs429774, rs2305742, rs11575934, rs375947, and rs401502 (the last three SNP listed are frequently linked, and are referred to in the literature as the "RTR haplotype" (129)). The disease susceptibilities associated with these SNPs are represented in Fig 4C, and include infectious disease, cancer, pediatric asthma and dermatological disease.

Infectious Disease (ID): Four infectious diseases (ID) that are influenced by *IL12RB1* polymorphism include tuberculosis (TB), malaria, leptospirosis and measles. TB is caused by the intracellular bacterium *Mycobacterium tuberculosis*; the factors that govern TB susceptibility in otherwise healthy, immunocompetent individuals are not well understood. Akahoshi et al. (130) demonstrated that TB patients from Kyushu Island, Japan were more likely to have the RTR haplotype (rs11575934, rs375947, and rs401502) compared to healthy unrelated controls. This susceptibility associated with the RTR haplotype conferring less sensitivity to IL12/IL23 *in vitro*; a follow up study demonstrated those patients with the RTR haplotype were also more likely to go on to develop severe TB (131). A similar study in Casablanca, Morocco also identified c.641G (rs11575934) and c.1094C (rs375947)) as associating with pulmonary TB susceptibility (132). Similar to TB resistance, resistance to malaria is also strongly supported by IL12 and IL12Rβ1 (133, 134). Malaria is mosquito-borne and caused by the protozoan *Plasmodium falciparum*, which after establishing its life cycle in the liver causes parasitemia in the blood. Zhang et al. (135) demonstrated that the

presence of the SNP rs383483 associated with extraordinarily high parasitemia (>10^4 parasites per μL blood); conversely, the rs429774 SNP was protective (135). Leptospirosis is a zoonotic disease caused by spirochetes of the *Leptospira* genus; following their binding to vascular cadherins (136), leptospira take up residence in multiple tissues and cause both mild and severe disease manifestations (e.g. liver dysfunction, myocarditis). Among individuals living on the Azores archipelago (Portugal), Esteves et al. (137) reported that the rs401502 allele conferred susceptibility to pathogenic leptospira. Finally, unlike TB, malaria or leptospirosis, measles is of viral origin (a paramyxovirus of the genus Morbillivirus) and is vaccine-preventable. The measles vaccine (MMR) depends on generation of neutralizing antibody; IL12's positive effects on antibody generation has been expertly reviewed (138). In individuals with the rs372889 allele, MMR-elicited antibody levels are significantly lower (139, 140). The significance of this result is all the greater given the prevalence of rs372889 in multiple ethnicities (Fig 4B).

Cancer (CA): While IL12 responsiveness during infectious disease is primarily associated with host resistance, the roles of IL12 in cancer (CA) are less circumscribed, and are dependent on the cancer specified. On the one hand, IL12 is a potent inhibitor of tumor angiogenesis (141, 142); on the other hand, IL12 drives T cell exhaustion in patients with B cell non-Hodgkin lymphoma (143). Among African American women, the SNP rs375947 associates with estrogen receptor (ER)-negative breast cancer risk (144); among women living in the Seattle-Puget Sound region, the risk of cervical adenocarcinoma is associated with the SNP rs11575934 (145). Individuals with non-Hodgkin lymphoma are more likely to have the rs2305742 SNP (146).

Pediatric Asthma (PA): The development of pediatric asthma (PA) is influenced by both inherited and environmental factors, and is diagnosed following one or more adverse respiratory events in response to an allergen (147). These respiratory events are the consequence of aeroallergen sensitization early in life (148–151), are mediated by IgE-dependent activation of airway eosinophils, neutrophil recruitment (152, 153), and are exacerbated by respiratory viral infection (154). A common feature among PA pathophysiology models is that certain combinations of heredity and environment bias PA patients' T_H cells to be more T_H2-like (leading to eosinophilia) or T_H17-like (leading to neutrophilia) relative to non-asthmatics (147, 155). Among the polymorphic genes that affecting asthma susceptibility in European American is *IL12RB1* (156, 157). Among children with asthma in Osaka, Japan there is a significant association between asthma risk and c.-111A>T (rs393548) (116).

Dermatological disease: Dermatological diseases effected by *IL12RB1* polymorphism include atopic dermatitis and hidradenitis suppurativa. Atopic dermatitis a relapsing inflammatory condition characterized by itch and eczema; similar to asthma, atopic dermatitis is associated with a predisposition to IgE-driven degranulation following exposure to otherwise innocuous allergens. As with asthma, atopic dermatitis is also associated with the rs393548 SNP among children in Osaka, Japan (116); the rs436857 SNP is also likely to be present in the same population (116). Even less well understood than atopic dermatitis is hidradenitis suppurativa, an inflammatory condition characterized by

painful cysts near the sweat glands. Using genomic DNA from a large cohort of patients with hidradenitis suppurativa, Giatrakos et al. (158) recently demonstrated that the certain combinations of the rs429774, rs375947 and rs401502 polymorphisms (which they define as "h1 and h2" haplotypes) associates with more advanced hidradenitis suppurativa and involvement of a greater number of skin areas.

IL12RB1 sequence variability at the mRNA splicing level—The studies reviewed above demonstrate that genomic polymorphism introduces variability in IL12Rβ1 function and disease susceptibility. In addition to genomic polymorphism, alternative splicing is another mechanism by which variability inIL12Rβ1 function is introduced (159, 160). Alternative splicing is used by humans and mice to introduce functional variability to multiple cytokine receptors (161). Here we review the data specific to human *IL12RB1* alternative splicing (Fig 4D) and mouse *il12rb1* alternative splicing (Fig 3), and highlight where similarities and differences exist between mice and humans.

Alternative splicing of mouse il12rb1: That mouse *il12rb1* mRNA is subjected to alternative splicing was first demonstrated by Ueli Gubler as part of his teams' identification and characterization of the mouse IL12 receptor (78). Using human IL12RB1 cDNA as a probe to identify its counterpart in mouse ConA blasts, Chua et al. (78) identified two clones ("clone 2" and "clone 3") that differed from one another in their C-terminus as a consequence of alternative splicing: whereas clone 2 contained all 16 exons, clone 3 is produced by a skipping of exon 14, which results in both a loss of the transmembrane domain and a frame shift mutation (Fig 3). Despite their sequence differences, when both clone 2 and clone 3 were individually transfected into COS-7 cells, both proteins bound extracellular IL12 with similar affinities (clone 2, K_d=899 pM; clone 3, K_d=1.3 nM); both proteins could also be immunoprecipitated from the cell surface of transfectants in complex with IL12. Clone 2 eventually became what is referred to as mouse IL12Rβ1. Clone 3, on the other hand, remained unstudied for some time afterward; until our own studies, Clone 3's only mention in the literature was by Showe et al. (162), who observed its expression (therein referred to as "β1b") in the spleens of BCG/LPS treated animals.

Our interest in mouse Clone 3/β1b stemmed from observing its expression in mouse dendritic cells following their encounter with *M. tuberculosis* (159). Prior to their exposure to *M. tuberculosis* and other proinflammatory stimuli, DCs preferentially express the IL12Rβ1 isoform; afterwards, both IL12Rβ1 and Clone 3 are expressed. The significance of this lay in that Clone 3, which we renamed "IL12Rβ1ΔTM", enhanced IL12p40-dependent DC migration to the draining lymph nodes (a process that is important for activation of *M. tuberculosis*-specific T_H cells). However, that IL12Rβ1ΔTM's enhancement was IL12Rβ1-dependent suggests that IL12Rβ1 is the more immunologically "dominant" of the two isoforms. Consistent with Chua et al. (78), we observed IL12Rβ1ΔTM protein to be membrane associated and, when overexpressed in otherwise *il12rb1*$^{-/-}$ cells, to be detectable on the cell surface as measured by flow cytometry. We have recently turned our attention to whether IL12Rβ1ΔTM also enhances IL12p40-dependent responses of T_H cells, as T_H cells must express *il12rb1* to limit experimental tuberculosis (117). The results of

these experiments are forthcoming, but are consistent with a model wherein IL12Rβ1ΔTM expression serves to potentiate mouse leukocytes' responses to IL12 (163).

Alternative splicing of human IL12RB1: Human *IL12RB1* mRNA is subjected to much more extensive alternative splicing than mouse *il12rb1* mRNA: whereas mouse leukocytes produce two alternative splice variants, human leukocytes produce at least thirteen (160). This diverse collection of splice variants is depicted in Fig 4D. Among these 13 isoforms, the most abundantly expressed are IL12Rβ1 (which corresponds to clone 5 of the original study by Chua et al. (65)) and another we refer to simply as "Isoform 2". Similar to mouse IL12Rβ1ΔTM, human Isoform 2 also has a unique C-terminus that lacks a transmembrane domain. It at this point, however, the similarity between mouse IL12Rβ1ΔTM and human Isoform 2 ends. Below is a summary of the salient features distinguishing mouse IL12Rβ1ΔTM and human Isoform 2 in terms of their origin, regulation, localization and function, as based on our studies using mouse (159) and human (160) tissues:

- Origin of human *IL12RB1* Isoform 2. Human Isoform 2 is produced by the use of an alternative exon (termed exon 9b) and alternative 3′ UTR (Fig 4D); this is unlike mouse IL12Rβ1ΔTM, which is produced by simply skipping of *il12rb1* exon 14 (Fig 3). Similar to mouse IL12Rβ1ΔTM, human Isoform 2 lacks a transmembrane domain and has a C-terminus unique from that of IL12Rβ1; however, the C-termini of mouse IL12Rβ1ΔTM and human Isoform 2 have no obvious homology to one another.
- Regulation of human *IL12RB1* Isoform 2. Human Isoform 2 is the predominant IL12RB1 isoform expressed by PBMCs, T_H cells, T_C cells and NK cells prior to their activation; following activation, IL12Rβ1 is preferentially expressed. This differs from mice, in which IL12Rβ1 is preferentially expressed prior to activation. Human lymphocytes' switch from Isoform 2-to-Isoform 1 is observed both *in vitro* (following PHA-stimulation) and *in vivo*, as the Isoform 1:Isoform 2 ratio is greater in the lungs of individuals with sarcoidosis (a disease characterized by the accumulation of activated lymphocytes) relative to control lungs unaffected by this disease.
- Localization of human *IL12RB1* Isoform 2. Human Isoform 2 localizes to an intracellular reticular network rather than the cell surface. While we initially hypothesized this reticulum represented the endoplasmic reticulum (ER), dual staining Isoform 2 cDNA transfectants for both Isoform 2 and protein disulfide isomerase proved otherwise; it was also undetectable in transfectants' supernatant (a feature of several cytokine receptor splice variants, which pass through the ER prior to being secreted (161)). Human Isoform 2's unique localization is likely due to its C-terminus, which is homologous to other intracellular membrane-associated proteins (e.g. syntaxins).
- Function of human *IL12RB1* Isoform 2. We are currently performing experiments to empirically determine human Isoform 2's function in the context of T_H cell function. However, based its intracellular localization (away from exogenous IL12), we predict Isoform 2 is either non-functional or serves to restrict IL12Rβ1's

localization to the cell surface (since IL12Rβ1 oligomerizes with itself, Isoform 2's homology to IL12Rβ1 may mean it too oligomerizes with IL12Rβ1). Should either of these predictions be correct, it would provide a rationale for why human T_H cells "switch" from preferential expression of Isoform 2 to IL12Rβ1 following activation (160), as IL12 and IL23 respectively sustain T_H1 and T_H17 cell survival (164, 165).

Collectively, the data above indicate that the variability in *IL12RB1* transcription, sequence and function is introduced by three factors: epigenetic modification, genomic polymorphism, and alternative splicing. Epigenetic modifications affecting *IL12RB1* transcription include IRF1 levels and the extent of histone methylation. Genomic polymorphism is a factor affecting both coding and non-coding portions of the IL12RB1 gene; although early studies tied *IL12RB1* polymorphism to infectious disease susceptibility, a growing number of studies link IL12RB1 polymorphism to non-infectious diseases including cancer, pediatric asthma and dermatological disease. Alternative splicing is an additional factor governing *IL12RB1* mRNA sequence, the balance of which controls whether *IL12RB1* is expressed as a signaling isoform (IL12Rβ1) or as an intracellular isoform located away from IL12/IL23 (Isoform 2). Each individual *IL12RB1*'s expression and function is likely influenced by these three factors in a combinatorial manner. If the past is any indicator, associations between *IL12RB1* polymorphism and disease-susceptibility are likely to continue expanding beyond infectious diseases; where there remains "fertile ground" for exploration is whether disease-susceptibility also associates with the extent to which *IL12RB1* mRNA is alternatively spliced or post-transcriptionally modified in any other manner.

The future of IL12p40 and IL12Rβ1's relationship

Given the significance of IL12 and IL23 to human health, IL12Rβ1 biology is primarily studied in in the context of IL12/IL23-dependent immune responses. However, the recent discovery of multiple novel IL12p40-heterodimers by Abdi et al. (166) demonstrates that IL12p40's binding partners are not restricted to IL12p35 or p19. Using serum from LPS-injected mice, Abdi et al. immunoprecipitated IL12p40-containing complexes and used mass spectrometry to identify novel IL12p40 binding partners ($IL12p40^{-/-}$ serum was used as a negative control). Their results demonstrate that *in vivo*IL12p40 has nineteen previously unknown binding partners, including CD5 Ag-like protein, Clusterin, and LPS-binding protein. Moreover, Abdi et observed that IL12p40-monomer can complex with extracellular p35 to form bioactive IL12; prior to their findings, the exclusive model was that IL12p40- and p35 had to be expressed by the same cell to form bioactive IL12. The results of Abdi et al. are an important advance in our knowledge of IL12p40, as it suggests that IL12p40 monomer (the primary form secreted by cells) is not secreted to suppress immunity per se (167), but rather is – using the terminology of Abdi et al. – a "poly functional adaptor" protein lying in wait for a binding partner. This model is consistent with the notion that IL12p35 expression is the rate limiting step of IL12-dependent immune responses (168). Given that IL12Rβ1 is the only known receptor for human IL12p40, it also suggests that IL12Rβ1 is involved in other signaling pathways that have yet to be discovered.

Among the myriad of proteins involved in human immunity, IL12p40 and IL12Rβ1 are inextricably linked. Here we have revisited the early data underlying our basic

understanding of IL12Rβ1 and its ability to promote anti-mycobacterial immunity, reviewed the clinical and pre-clinical data supporting IL12Rβ1's involvement in promoting autoimmunity, and surveyed the epigenetic, genomic, and mRNA-splicing mechanisms through which inter-individual variability in *IL12RB1* transcription and sequence are introduced. In addition to understanding how these mechanisms function alone or in combination effect IL12/IL23 responsiveness and disease susceptibility, we must also begin teasing apart the function of additional IL12p40-containing cytokines members and their relation to IL12Rβ1 and disease-susceptibility. Given how much we still need to learn about IL12p40/IL12Rβ1 and their encoding genes, the future of IL12p40 and IL12Rβ1's relationship is bright.

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- Human *IL12RB1* is a gene that contributes to both health and disease
- Sequence diversity is introduced into *IL12RB1* at both gDNA and mRNA levels
- *IL12RB1* sequence diversity leads to individual variability in IL12/IL23 sensitivity
- We review how *IL12RB1* sequence diversity contributes to disease susceptibility

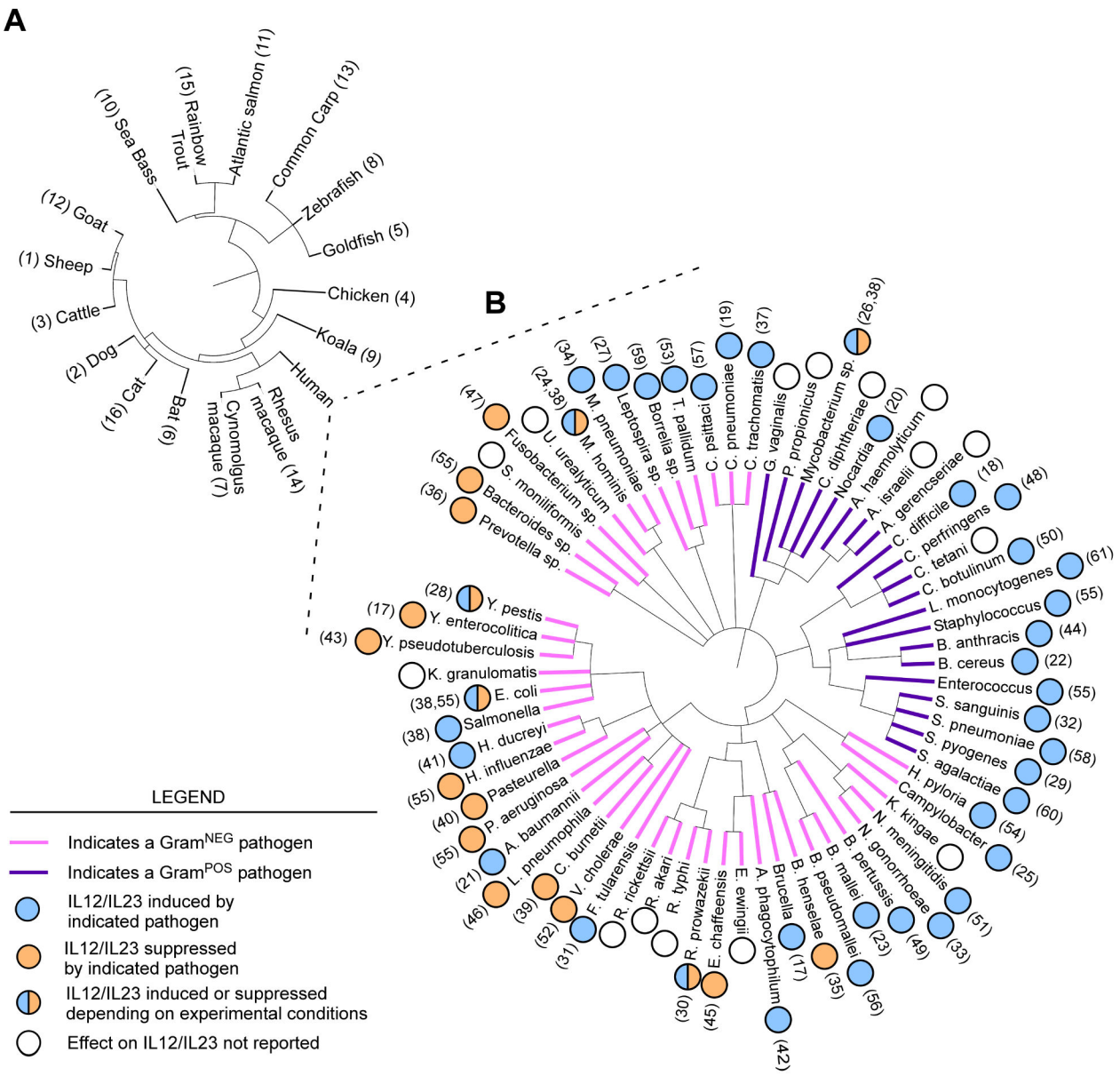

FIGURE 1.

The IL12Rβ1-dependent cytokines IL12/IL23 are expressed by multiple vertebrate species in response to their natural pathogens. (**A**) Seventeen vertebrate species are known to express IL12/IL23 in response to pathogen challenge; depicted are the phylogenetic relationships between these seventeen species (*Dicentrarchus labrax*, Sea Bass; *Oncorhynchus mykiss*, Rainbow trout; *Salmo salar*, Atlantic salmon; *Cyprinus carpio*, Common Carp; *Danio rerio*, Zebrafish; *Carassius auratus auratus*, Goldfish; *Gallus gallusdomesticus*, Chicken; *Phascolarctos cinereus*, Koala*; Homo sapiens*, Human; *Macacamulatta*, Rhesus Macaque; *Macacafascicularis*, Cyno Macaque; *Rousettus leschenaultia*, Bat; *Felis catus*, Cat; *Canis familiaris*, Dog; *Bos taurus*, Cattle; *Ovis aries*, Sheep; *Capra aegagrus hircus*, Goat) alongside a reference (1–16) demonstrating that species' IL12/IL23 expression in response to one or more natural pathogens. (**B**) Among

bacterial pathogens of humans, IL12/IL23 elicitation is associated with species' Gram staining pattern. Depicted are the phylogenetic relationships between sixty-six bacterial species that are etiological agents of human disease; $Gram^{NEG}$ species are indicated by pink branches, while $Gram^{POS}$ species are indicated by purple branches. Adjacent to each species is a circle that is either colored blue (indicating a pathogen that elicits IL12/IL23 expression), orange (indicating a pathogen that suppresses IL12/IL23 expression), blue and orange (indicating the pathogen's effect on IL12/IL23 expression is variable depending on the experimental system), or white (indicating the pathogen's effect on IL12/IL23 expression has not been reported). The number adjacent to each circle indicates the reference (17–61) demonstrating whether the pathogen elicits or suppresses IL12/IL23 expression. The phylogenic trees shown in (**A**) and (**B**) were generated using Interactive Tree of Life (iTOL) (169).

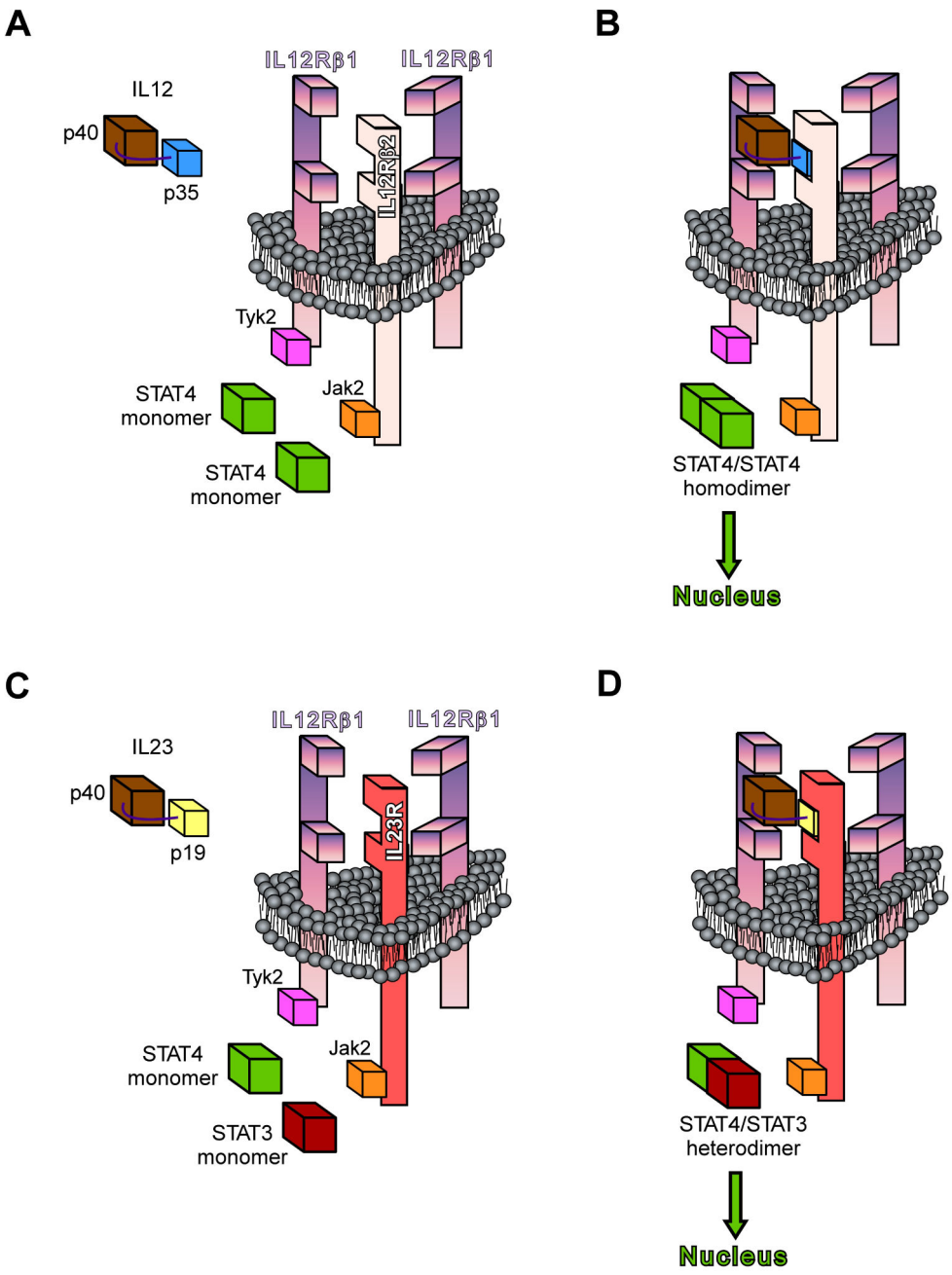

FIGURE 2.

IL12Rβ1 contributes to both the IL12- and IL23-signaling pathways. (**A–B**) The IL12 signaling pathway comprises the cytokine IL12 (a disulfide-linked heterodimer of the proteins p40 and p35), the type 1 transmembrane proteins IL12Rβ1 and IL12Rβ2, the intracellular pre-associated kinases Tyk2 (which associates with IL12Rβ1) and Jak2 (which associates with IL12Rβ2), and intracellular STAT4. (**A**) Prior to IL12's engagement with IL12Rβ1 and IL12Rβ2, STAT4 exists in monomeric form and is inactive as a transcription factor. (**B**) After IL12's engagement with IL12Rβ1 (via its p40 domain) and IL12Rβ2 (via its p35 domain), Tyk2 and Jak2 phosphorylate STAT4, results in STAT4/STAT4

homodimer formation. This homodimer translocates to the nucleus, where it serves as a transcription factor for multiple genes associated with T_H1 development. (**C–D**) The IL23 signaling pathway comprises the cytokine IL23 (a disulfide-linked heterodimer of the proteins p40 and p19), IL12Rb1 and IL23 (also a type 1 transmembrane protein), Tyk2 (which associates with IL12Rβ1) and Jak2 (which associates with IL23R), STAT4 and STAT3. (**C**) Prior to IL23's engagement with IL12Rb1 and IL23R, STAT4 and STAT3 exists in monomeric forms and are inactive as a transcription factor. (**D**) After IL23's engagement with IL12Rβ1 (via its p40 domain) and IL12Rβ2 (via its p19 domain), Tyk2 and Jak2 phosphorylate STAT4 and STAT3, results in STAT4/STAT3 heterodimer formation. This heterodimer translocates to the nucleus, where it promotes the transcriptional signature associated with T_H17 development.

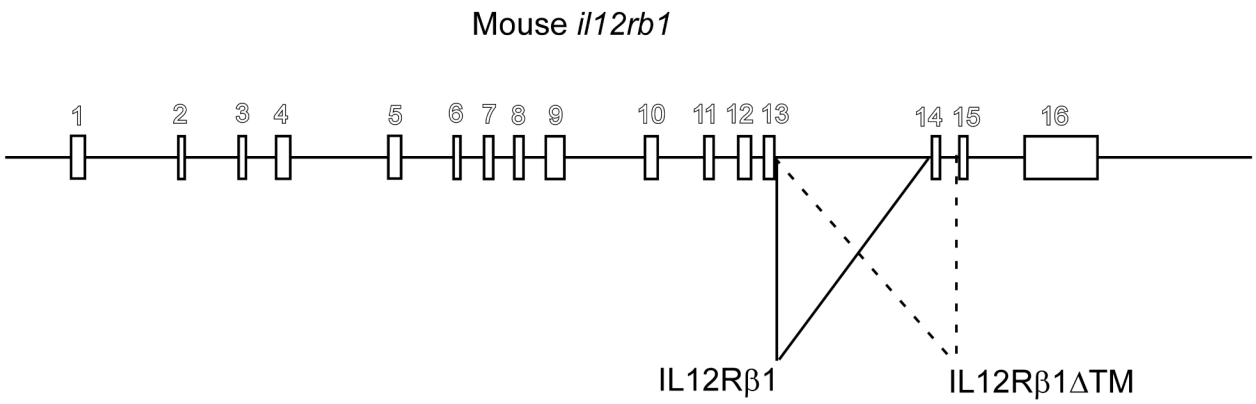

FIGURE 3.

The organization of the mouse *il12rb1* gene. *il12rb1* is located on mouse chromosome 8, and comprises sixteen exons. As depicted by the solid lines under *il12rb1*, the IL12Rβ1 isoform is generated via inclusion of all sixteen *il12rb1* exons, including exon 14 which encodes IL12Rβ1's transmembrane domain. As depicted by the hatched lines under *il12rb1*, IL12Rβ1ΔTM is generated by inclusion of exons 1-13 and skipping of exon 14. IL12Rβ1ΔTM has also been referred to in the literature as "clone 3" by Chua et al. (78) and "β1b" by Showe et al. (162).

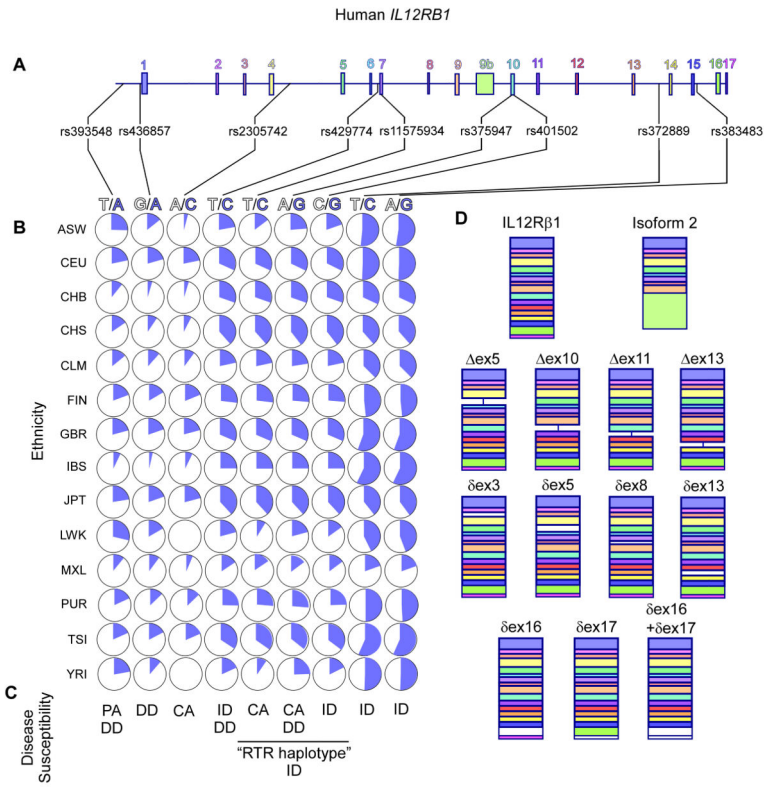

FIGURE 4.

Human *IL12RB1* sequence variability is introduced at the genomic polymorphism and mRNA-splicing level. (**A**) Human *IL12RB1* is located on the p-arm of chromosome 19, and comprises exons 1-9, 9b, and 10-17. Depicted along the length of *IL12RB1* are the location and relative sizes of each exon and intron, as well as the approximate location of nine polymorphic sites that are present in multiple ethnicities at varying frequency (rs393548, rs436857, rs2305742, rs429774 (135), rs11575934, rs375947, rs401502, rs372889, rs383483). (**B**) Listed under each polymorphism is the nature of the polymorphic site: the major nucleotide present at each site (i.e. the nucleotide present in the majority of humans at that site) is on the left in white font, while the minor nucleotide present at each site (i.e. the nucleotide present in the minority of humans at that site) is on the right in blue font. Beneath each major/minor nucleotide listing are 14 pie graphs that represent the frequency of major and minor polymorphism in 14 different ethnicities (ASW, Americans of African Ancestry in Southwest US; CEU, Utah Residents with Northern and Western European ancestry; CHB, Han Chinese in Beijing, China; CHS, Southern Han Chinese, China; CLM, Colombians in Medellin, Colombia; FIN, Finnish in Finland; GBR, British in England and Scotland; IBS, Iberian Populations in Spain; JPT, Japanese in Tokyo, Japan; LWK, Luhya in Webuye, Ken; MXL, Mexican Ancestry fro; PUR, Puerto Ricans from; TSI, Toscani in Italia; YRI, Yoruba in Ibadan, Nigeria); frequency data were collected by the 1000 Genomes Project (170) and are publically available via the NCBI 1000 Genomes Browser (http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes). As with the nucleotide listings above the pie graphs, major polymorphisms are depicted by the white sector of each pie chart, while minor polymorphisms are depicted by the blue sector of each pie chart. (**C**)

Corresponding to each of the polymorphisms indicated in (A) are reports of its association with disease susceptibility or outcome; listed below each polymorphism is whether this is an infectious disease (ID), cancer (CA), pediatric asthma (PA) or dermatological disease (DD). The literature references supporting these assignments are described in the article text and reproduced here: rs393548 (116), rs436857 (116), rs2305742 (146), rs429774 (135, 158), rs11575934 (130, 145), rs375947 (130, 144, 158), rs401502 (130, 137), rs372889 (139, 140), rs383483 (135). Given that rs11575934, rs375947, and rs401502 are frequently linked, they are often referred to in the literature as the "RTR haplotype" (129) (**D**) Depicted are the thirteen alternative splice variants expressed in human PBMCs and lung tissue. Each individual splice variant is depicted as a combination of colors; each color corresponds to the encoding exon as depicted in (**A**). The names assigned to each isoform correspond to the names used by Ford et al. (160); as depicted by their being at the top, IL12Rβ1 and Isoform 2 are the most abundantly expressed *IL12RB1* isoforms in human cells and tissues.