Genetics of Interleukin 1 Receptor-Like 1 in Immune and Inflammatory Diseases

Loubna Akhabir and Andrew Sandford*

Department of Medicine, University of British Columbia, UBC James Hogg Research Centre, Providence Heart + Lung Institute, Room 166, St. Paul’s Hospital, 1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada

Abstract: Interleukin 1 receptor-like 1 (IL1RL1) is gaining in recognition due to its involvement in immune/inflammatory disorders. Well-designed animal studies have shown its critical role in experimental allergic inflammation and human in vitro studies have consistently demonstrated its up-regulation in several conditions such as asthma and rheumatoid arthritis. The ligand for IL1RL1 is IL33 which emerged as playing an important role in initiating eosinophilic inflammation and activating other immune cells resulting in an allergic phenotype.

An IL1RL1 single nucleotide polymorphism (SNP) was among the most significant results of a genome-wide scan investigating eosinophil counts; in the same study, this SNP associated with asthma in 10 populations.

The IL1RL1 gene resides in a region of high linkage disequilibrium containing interleukin 1 receptor genes as well as interleukin 18 receptor and accessory genes. This poses a challenge to researchers interested in deciphering genetic association signals in the region as all of the genes represent interesting candidates for asthma and allergic disease.

The IL1RL1 gene and its resulting soluble and receptor proteins have emerged as key regulators of the inflammatory process implicated in a large variety of human pathologies. We review the function and expression of the IL1RL1 gene. We also describe the role of IL1RL1 in asthma, allergy, cardiovascular disease, infections, liver disease and kidney disease.

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INTRODUCTION

Interleukin 1 receptor-like 1 (IL1RL1), also called T1, ST2, DER4 and FIT-1, is a member of the interleukin 1 super-family [1] but does not bind interleukin 1 (IL1) [2]. IL1RL1 was an orphan receptor until the description of its ligand, interleukin-33 (IL33) in 2005 [3]. Since then, IL33 binding to IL1RL1 has been associated with a variety of disease states and in particular to inflammatory processes as outlined in recent reviews [4, 5]. In the present review, we will focus mainly on the genetic associations of IL1RL1 with disease.

IL1RL1 GENE AND PROTEINS

The IL1RL1 gene is located in chromosome 2q12 and is composed of 11 exons [6]. A number of IL1 family members reside in the immediate vicinity of the IL1RL1 gene namely IL1R2, IL1R1, IL1RL2, IL18 receptor 1 (IL18R1) and IL18 receptor accessory protein (IL18RAP). The region spans about 300 kb and is in high linkage disequilibrium (LD) (Fig. 1). There is evidence for the involvement of the genes surrounding IL1RL1 in human and experimental disease, and therefore the causal locus responsible for genetic association signals from this region is difficult to determine.

*Address correspondence to this author at the Department of Medicine, University of British Columbia, CBC James Hogg Research Centre, Providence Heart + Lung Institute, Room 166, St. Paul’s Hospital, 1081 Burrard Street, Vancouver, B.C., V6Z 1Y6, Canada; Tel: (604) 806-9008; Fax: (604) 806-8351; E-mail: Andrew.Sandford@hli.ubc.ca

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corresponds to the extra-cellular domain of IL1RL1 isoform A except for nine amino-acids in the C-terminal region.

IL1RL1 isoform A is mainly expressed on cells of hematopoietic provenance, mainly T cells [20]. It has been shown that binding of IL1RL1 isoform A with its ligand on the surface of basophils, eosinophils and mast cells promotes their activation [21], increased adhesion and survival [22] and degranulation [23], respectively. IL33/IL1RL1 isoform A has also been shown to play a role in activating macrophages [24, 25].

The short form, IL1RL1 isoform B, is expressed by various cells including epithelial cells, endothelial cells, fibroblasts and smooth muscle cells. This expression is augmented upon stimulation with IL1α, IL1β, TNFα, LPS and other factors inducing cell stress such as cardiac infarction and hypoxia [26]. The tissue distribution of IL1RL1 isoform B seems to be relatively ubiquitous, with the highest levels of the secreted form found in the lung followed by the heart and the brain [27].

Several studies show that the membrane-bound IL1RL1 protein acts as a specific marker for Th2 cells [20]. In vitro blockade of IL1RL1 signaling with recombinant IL1RL1 protein to compete with the endogenous receptor resulted in the abrogation of differentiation to and activation of Th2, but not Th1, effector cells [28]. Interestingly, IL1RL1 has been found to play a considerable role in a newly discovered immune type2 effector leukocytes, known as nuocytes [29]. An IL13-GFP mouse model was utilized to define these as cells not corresponding to a previously known leukocyte lineage that express ICOS, IL1RL1 and IL25R [29]. The nuocytes’ function included the innate immune response to helminth infection with *Nippostrongylus brasiliensis* by secretion of high levels of IL13 in response to IL25 and IL33.

The ligand for IL1RL1 is a recently discovered member of the interleukin 1 family: IL33 [3]. The signaling of IL1RL1 isoform A binding to IL33 results in the activation of the Mitogen-Activated Protein kinases ERK1, ERK2 and p38 and the subsequent activation of NFκB [3, 23]. IL1RL1 isoform B corresponds to the extra-cellular domain of isoform A and *in vitro* studies have shown that it can also bind IL33 and act as a decoy receptor inhibiting the activation of NFκB [30] and the subsequent inflammatory response. This was confirmed in an animal model where introduction of soluble IL1RL1 decreased pro-inflammatory cytokine (IL4, IL5 and IL13) production in a murine asthma model after treatment with IL33. It was shown that this protective effect of the soluble IL1RL1 seems to be IL10 dependent in an animal model of ischemia reperfusion injury [31].

**Fig. (1).** Linkage disequilibrium in IL1RL1 and surrounding genes on chromosome 2q12 (102280 kb to 102500 kb) in the CEU HapMap population.
Asthma and other Respiratory Diseases

Increased eosinophil count is a phenotype associated with the majority of asthma cases and correlates with severity of the disease as well as response to glucocorticoid treatment [32]. Using asthma mouse models, it was shown that eosinophilic inflammation is significantly decreased following allergic stimuli in animals subjected to treatments with recombinant IL1RL1 or antibodies directed against the membrane-anchored protein [33, 34]. Soluble IL1RL1 has been shown to be sufficient to reduce experimental allergic airway inflammation using an intravenous IL1RL1 gene transfer mouse model [34], perhaps by acting as a decoy receptor. In addition, a ST2−/− knockdown mouse model of asthma showed decreased airway inflammation [35].

IL1RL1 expression has been shown to increase in murine [35] and human [36] asthmatic lungs; soluble IL1RL1 has been shown to increase in the serum of asthmatic patients during acute attacks, and this increase correlated with lung function decrease as well as an increase in the serum levels of the inflammatory cytokine IL5 [37]. Other in vivo studies of airway allergic inflammation demonstrated a clear involvement of soluble IL1RL1 protein in regulating a Th2 response after allergen challenge [35] as well as in the resolution of allergen-induced inflammation as assessed by airway hyper-responsiveness [38].

Since the late 1990s, genetic studies have shown linkage of chromosome 2 with asthma, lung function (as assessed by FEV1/VC, a common clinically-useful index for airflow limitation), eosinophilia and IgE levels [39-41].

Polymorphisms in IL18R1, a gene in tight LD with IL1RL1, were associated with asthma, atopic asthma and airway hyper-responsiveness using a candidate gene approach in a Danish population and the association consistently replicated in two other European populations [18]. In the same year, another candidate gene association study documented significant genetic association of the gene cluster containing IL1RL1, IL18R1 and IL18RAP with asthma and atopy in a Dutch population [19]. Additional association evidence was reported by the same group using pathway analysis to detect gene-gene interactions in the Toll Like Receptor (TLR)-related pathway. IL1RL1 isoform B has been shown to down-regulate gene expression of TLR4 and TLR1 in vitro after treatment with LPS and in vivo in a LPS-induced shock mouse model [42].

Twenty-nine genes implicated in TLR regulation were selected for a pathway analysis in Dutch populations [43]. IL1RL1 SNPs were associated with allergy and asthma phenotypes as single SNPs although the significance did not survive multiple testing correction. In addition, when gene x gene interactions were tested using the multifactor dimensionality reduction approach, IL1RL1 SNPs were identified as interacting factors in analyses of IgE phenotypes [43].

In a study performed by our group in collaboration with others, we investigated three Canadian and one Australian populations but failed to detect any significant association with IL1RL1 that survived correction for multiple comparisons [44]. The same cohorts, in addition to one American population, were used in an association study of genes in the vitamin D pathway with asthma and atopy phenotypes. IL1RL1 SNPs were selected for this study based on the fact that IL1RL1 was shown to be transcriptionally regulated by vitamin D [45]. The genotyping covered more variants of IL1RL1 than the initial study and the number of candidate genes was substantially less (11 versus 120 genes). Significant associations of these variants were observed with asthma and atopy phenotypes [46].

Given the role of eosinophils in the pathogenesis of asthma, alleles that associate with increased eosinophil count could be detrimental in terms of asthma risk and severity. In a Genome Wide Association Study (GWAS) of eosinophil count in an Icelandic population, a SNP in IL1RL1 (rs1420101) showed the most significant association. The A allele of rs1420101 associated with increased eosinophil count and in further analyses with increased serum IgE as well as with three asthma phenotypes (asthma, atopic asthma, non atopic asthma) in nine European populations and one East Asian population [47], rs1420101 is an intrinsic SNP which is in high LD (r² greater than 80%) with a large number of other variants in IL1RL1, IL18R1 and IL18RAP; this group of SNPs contains mostly intronic SNPs in addition to a coding-synonymous and a few 3’ and 5’ UTR SNPs. No functional studies have been performed thus far to determine the association-causing SNP.

It is of note that an association of a SNP in IL33 (rs3939286) with eosinophil count, asthma and atopic asthma was reported in same study, although the IL33 association with eosinophil count did not reach genome-wide significance. The same IL33 SNP was associated with nasal polypsis in a Belgian population in a candidate gene study [48].

Wu et al. used GWAS data of childhood asthma in a Mexican population [49] to perform a candidate gene analysis. In this study, 237 genes were selected from human and animal model published studies of asthma to have at least one SNP associated with an asthma phenotype. They reported IL1RL1 among the most significant associations. Furthermore, their results were subjected to multi-marker analysis, which confirmed IL1RL1 as a significant finding as well as IL18RI.

Collectively, there is strong evidence for genetic association of IL1RL1 with asthma and related phenotypes. This association is certainly very well supported by the biology of IL1RL1 and related proteins. IL33 is secreted by the airway epithelium in response to stress such as allergens or viruses, and binds to IL1RL1 isoform A on the surface of immune cells. There are excellent reviews about the central role of the epithelium in initiating and sustaining immune responses [50]. IL33/IL1RL1 isoform A plays a crucial role in that process.

The binding of IL1RL1 isoform A and its ligand IL33 triggers the NFκB signaling pathway, which leads to the transcription of cytokines needed for a Th2 immune response. However, the role of IL1RL1 isoform B remains unclear. Several animal models and in vitro studies show that IL1RL1 isoform B prevents the IL33/IL1RL1 isoform A signaling and consequently attenuates inflammation, indicat-
ing its role as a negative regulator of the pro-inflammatory IL33/IL1RL1 isoform A axis. Human data on the other hand clearly demonstrate a consistent increase of IL1RL1 isoform B in an array of pathological conditions as well as the correlation of this increase with severity. Additionally, there was a report of an animal study showing that mice deficient in IL1RL1 showed attenuated airway inflammation after challenge with an allergen [51], suggesting that IL1RL1 isoform B might be participating in the excessive inflammation observed in asthma. However, the model used for this study was the transgenic TCR-mouse model; these animals are predisposed to autoimmune disorders because they carry rearranged TCR α and β genes from a diabetogenic T cell clone.

The above studies do not seem to be consistent with the antagonist role of IL1RL1 isoform B but rather indicate a possible involvement in the pathology. An alternative explanation would be that the increase of IL1RL1 isoform B is a means of preventing an exaggerated immune response but either occurs too late or is insufficient to remedy to the pathological state.

Evidently, soluble IL1RL1 plays a role in the regulation of the immune response, notably in severe disease. Exactly what that role is and the mechanisms underlying it need to be clarified in order to develop efficient strategies for developing therapeutics using the IL1RL1 proteins.

Recent human data in Chronic Obstructive Pulmonary Disease (COPD) seem to indicate an involvement of soluble IL1RL1 in the early stages of COPD [52]. This study however involved a small number of patients and needs replication.

**Allergy and Immune Disorders**

A SNP in the distal promoter region of IL1RL1, rs6543116 (-26999G/A), was associated with increased risk for atopic dermatitis and up-regulation of gene expression [53]. This study suggested a functional effect of rs6543116 as the A allele correlated with an up-regulation of the gene transcription as well as serum levels. The same group reported the association of serum levels of IL33 and SNPs in the IL33 gene with Japanese cedar pollinosis, the most common form of allergic rhinitis in Japan [54]. In addition, Cas­tano et al. found a protective association of IL1RL1 SNPs with chronic rhinosinusitis using a cohort of surgery-unresponsive chronic rhinitis patients, this association was stronger in more severe disease [55].

IL33 signaling through IL1RL1 was shown to be involved in anaphylactic shock in an animal model study examining the response of IgE-sensitized mice to IL33 treatment [23]. The same authors had shown elevated IL33 levels in the serum of atopic patients undergoing surgery; this effect was demonstrated to derive purely from innate immunity as T or B cells were not required. The pathological effect could be prevented by treatment with anti-IL33 antibody or soluble IL1RL1 and was not observed in ST2+ animals [23].

IL1RL1 and closely linked genes have been implicated in an array of autoimmune diseases. Levels of IL1RL1 isoform B have been shown to be increased in various conditions such as Systemic Lupus Erythematosus (SLE), sclerosis, and rheumatoid arthritis (RA) [56]. Mok et al. found that elevated serum IL1RL1 isoform B levels in SLE patients correlated with disease activity [57]. To date, GWAS performed in Chinese and European populations have not found association of IL1RL1 SNPs with RA [58, 59].

Studies in animal models demonstrated that recombinant IL1RL1 isoform B protein, or anti-IL1RL1 antibody could significantly attenuate the severity of experimental arthritis [60, 61] and IL1RL1 knock-out mice were shown to develop less severe form of disease and had reduced pro-inflammatory cytokine production. Additionally, human studies have shown increased levels of IL33 and IL1RL1 in RA synovium paralleling increased inflammation [62]. Studies in animal models strongly suggest that the involvement of IL33/IL1RL1 in RA is through triggering mast cell degranulation in the RA synovium [63]. Although there is good evidence for a role of IL33/IL1RL1 in human and experimental arthritis, no SNPs in these genes were found associated with susceptibility to RA in GWAS data [64].

The IL1RL1/IL33 signaling axis was implicated in inflammatory bowel disease (IBD) for the first time in two recent studies characterizing IL1RL1 and IL33 protein and mRNA expression in IBD patients [65]. There was an increase in soluble IL1RL1 levels in the gut, which was mainly associated with the active state of ulcerative colitis, indicating a possible negative regulation of the IL1RL1/IL33 pathway in order to dampen the inflammation. Pastorelli et al. confirmed the observation of elevated levels of IL1RL1 and IL33 in the serum and mucosa of IBD patients; they also showed that anti-TNF decreased IL1RL1 isoform A levels and increased the soluble isoform making more decoy receptor available in order to sequester IL33 and reduce the inflammation [66].

A SNP 1.5 kb downstream of IL18RAP (rs917997) was associated with susceptibility to IBD in a Dutch population; the same SNP was associated with celiac disease in three European populations [67]. rs917997 along with another SNP in the intergenic region between IL1RL1 and IL18R1 (rs13015714) were associated with celiac disease in a GWAS of a UK population [68]. The same SNP downstream of IL18RAP (rs917997) was associated with Crohn’s disease in a GWAS [69].

These genetic and mechanistic data suggest that IL1RL1/IL33 plays a role in the gut mucosa similar to the airway epithelium i.e. IL1RL1 isoform A/IL33 eliciting a Th2 immune response and IL1RL1 isoform B serving as a negative regulator.

There is evidence that IL1RL1 directly acts on macrophages to suppress their ability to produce pro-inflammatory cytokines [42]. Macrophages are instrumental in diabetes pathogenesis. In an animal model of diabetes (multiple low-dose streptozotocin-induced diabetes), Mensah-Brown et al. [70] showed that specific disruption of the IL1RL1 gene significantly enhanced inflammation in their mouse model as estimated by an increase in cellular infiltration in pancreatic islets and a reduction in cells immuno-positive for insulin. Recently, a genetic linkage study demonstrated linkage of chromosome 2 with type 2 diabetes with a LOD score of 4.5 [71]. Follow-up genetic studies are warranted to narrow
down the linkage signal and investigate specific SNP associations. This may lead to the identification of novel pathways in diabetes.

In summary, the available data on the involvement of IL1RL1 and its ligand IL33 in immune and autoimmune disorders are reasonably consistent; a clearer understanding of the balance between IL1RL1 isoform A/IL33, IL1RL1 isoform B/IL33 and its regulation is needed in order to make that axis a more attractive target for therapeutic intervention.

**Cardiovascular Disease**

In vitro and animal model studies have demonstrated that IL33/IL1RL1 isoform A signaling protects cardiomyocytes from apoptosis by suppressing Caspase 3 activity and promoting the expression of anti-apoptotic proteins in vitro and improves survival in experimental myocardial infarction (MI) animals [72]. Human studies have shown an increase of soluble IL1RL1 after myocardial stress or injury, and MI [26, 73]; the levels correlated with diastolic load [74], cardiac abnormalities on electrocardiogram (ECG) and poor prognosis in dyspneic and MI patients [75-77]. In a study following 150 patients admitted to hospital with acutely destabilized heart failure, multiple serum samples were collected between admission and discharge and soluble IL1RL1 levels were measured. The results showed that IL1RL1 isoform B levels were a powerful predictor of 90-day mortality. Indeed, IL1RL1 isoform B serum levels are considered a reliable biomarker for heart failure [78, 79] as delineated by a recent review by Moore et al. [80]. A more recent study demonstrated for the first time that IL1RL1 isoform B could be used to predict left ventricular and infarct recovery after acute MI [81].

The company Critical Diagnostics in collaboration with the Brigham and Women’s Hospital in Boston has developed a diagnosis kit called Presage that uses soluble IL1RL1 levels for diagnosis and prognosis of cardiovascular disease. However, this kit is not yet approved by the FDA for clinical use. Many U.S. and international patents protect the use of IL1RL1 for the diagnosis and prognosis in cardiovascular disease.

The fact that increased level of IL1RL1 is correlated with poor prognosis in different instances of cardiovascular disease points to a role of soluble IL1RL1 as marker for the severity of the immune response. Increased IL1RL1 isoform B is indicative of an overwhelming immune response that is hard to control and thus leads to unfavorable outcome in cardiovascular disease patients, such as after an MI.

**Infections**

IL1RL1 isoform B levels correlate with sepsis severity and outcome [82]. A possible mechanism was recently described by Alves-Filho et al. [83]. Using the cecal ligation and puncture model in Balb-c mice [83], a widely used model for experimental sepsis, this group demonstrated that IL33 treatment was protective from peritonitis and enhanced bacterial clearance. Their data also show that the protective effect of IL33 treatment was achieved via the inhibition of a TLR-signaling-induced protein, GRK2. GRK2 plays a prominent role in sepsis as it down-regulates CXCR2 (a receptor for IL8, a chemokine that attracts neutrophils to infection sites) thus leading to inefficient clearance of bacteria.

In agreement with the role of IL1RL1 proteins in the promotion of Th2 responses, mRNA levels of both receptor and soluble forms of the IL1RL1 transcript were shown to be up-regulated in an animal model of Toxoplasma gondii parasitic infection and this up-regulation correlated with protection from the infection [84]. In addition, ST2+/− knockout mice demonstrated increased susceptibility and more severe disease compared to wild type mice as assessed by weight loss, increased parasite transcript levels and typical disease pathology [84]. In 2008, a small study of a Somali population reported an association of a SNP in the 3’UTR of IL18R1 (rs3213733) with variability in Rubella vaccine-induced humoral immunity [85]. It is interesting that the same SNP was recently shown to be associated with asthma in two different studies, in Mexican and Japanese populations [47, 86]. As LD patterns differ between populations, this suggests a potential functional role of this SNP in regulating gene expression/function.

Additional evidence for a role of the IL33/IL1RL1 axis in host defense comes from an animal study showing the protective role of IL33 in intestinal infection with nematodes [87].

In summary, IL1RL1 confers protection from infection, which is consistent with its involvement in the Th2 immune response. The increase in IL1RL1 signaling skews T cells to Th2 and prevents a parasite-specific Th1 polarized response.

**Liver and Kidney Disorders**

In a candidate gene association study of the course of Hepatitis C in a Japanese population, 103 genes including IL1RL1 and IL18R1 were investigated [88]. SNPs in both these genes as well as other genes involved in immune responses were significantly associated with serum levels of alanine aminotransferase (ALT). ALT levels are routinely used as a diagnostic test of liver function and elevated levels are an indicator of infections and other disorders. Nevertheless, this group’s data were not corrected for multiple testing and need to be replicated in other populations.

An over-expression of IL1RL1 and IL33 mRNA in fibrotic liver was reported using mouse and human tissue sections [89].

**CONCLUDING REMARKS**

The IL1RL1 gene and its resulting soluble and receptor proteins have emerged as key regulators of the inflammatory process implicated in a large variety of human pathologies (see summary Table 1).

IL1RL1 is important for both innate and adaptive immunity as IL1RL1 isoform A binding with its ligand IL33 leads to polarization of T helper cells into Th2 and also activates and promotes the degranulation of mast cells. The resulting inflammation is down-regulated by the soluble form of IL1RL1; levels of the latter are recognized as biomarkers for the severity of various conditions. Except for the functional analysis of the IL1RL1 SNP rs6543116 associated with asthma and atopic dermatitis [36, 53], there has been no functional analysis of the disease-associated variants in
Table 1.

| Gene   | SNP      | Chr. Loc. | SNP Location | Disease/Phenotype          | pValue | Study                      | Population | N      | Refs                                      |
|--------|----------|-----------|--------------|-----------------------------|--------|----------------------------|------------|-------|-------------------------------------------|
| IL1RL1 | rs949963 | 102769786 | 5' near-gene | Childhood asthma            | 0.033  | Candidate gene study follow-up to GWAS | Mexican    | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL1R1  | rs3917289| 102781911 | intronic     | Childhood asthma            | 0.022  | Candidate gene study follow-up to GWAS | Mexican    | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL1RL1 | rs11685424| 102926981 | 5' near-gene | Childhood asthma            | 0.04   | Candidate gene study follow-up to GWAS | Mexican    | 492 cases + both parents | Reijmersink - Allergy 2010                |
| IL1RL1 | rs11685480| 102927086 | 5' near-gene | Specific IgE egg 1-2 years  | 0.02   | Candidate gene study gene-gene interaction analysis | Dutch    | 3062 children (birth cohort) | Shimizu et al. - Hum Mol Genet 2005       |
| IL1RL1 | rs6543116 | 102927726 | promoter     | Atopic dermatitis           | 0.000007 | Candidate SNP study             | Japanese   | 452 cases / 636 controls | Bossé et al. - Respir Res 2009          |
| IL1RL1 | rs1420089 | 102938389 | intronic     | Asthma                      | 0.033  | Candidate gene study            | French-Canadian founder population | 72 families | Bossé et al. - Respir Res 2009          |
| IL1RL1 | rs13431828| 102954653 | 5' UTR       | Chronic rhinosinusitis      | 0.008  | Candidate gene study            | French-Canadian | 206 cases / 196 controls | Castano et al. - Am J Rhinol Allergy 2009 |
| IL1RL1 | rs13431828| 102954653 | 5' UTR       | Childhood asthma            | 0.0002 | Candidate gene study follow-up to GWAS | Mexican    | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL1RL1 | rs1041973 | 102955468 | Cod.non.syn  | Atopy                       | 0.046  | Candidate gene study            | Canadian birth cohort | 98 families | Bossé et al. - Respir Res 2009          |
| IL1RL1 | rs1041973 | 102955468 | Cod.non.syn  | Course of hepatitis C       | 0.004  | Candidate gene study            | Japanese   | 238 cases | Saito et al. - Biochem Biophys Res Commun 2004 |
| Gene   | SNP       | Chr. Loc. | SNP Location | Disease/Phenotype      | pValue        | Study                      | Population | N             | Refs.                      |
|--------|-----------|-----------|--------------|------------------------|--------------|----------------------------|------------|-----------------|---------------------------|
| IL1RL1 | rs1041973 | 102955468 | Cod.non.syn  | Childhood asthma        | 0.00035      | Candidate gene study_follow-up to GWAS | Mexican    | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL1RL1 | rs1420101 | 102957716 | intronic     | Eosinophil count        | 5.3 x 10^-10 | GWAS                      | Icelandic  | 9392 individuals | Gudbjartson et al. - Nat Genet 2009 |
| IL1RL1 | rs1420101 | 102957716 | intronic     | Asthma                 | 5.5 x 10^-12 | Candidate gene study_follow-up to GWAS | 9 European + 1 East Asian populations | 7996 cases / 44890 controls | Gudbjartson et al. - Nat Genet 2009 |
| IL1RL1 | rs2160203 | 102960824 | 3' UTR       | Chronic rhinosinusitis | 0.03         | Candidate gene study       | French-Canadian | 206 cases / 196 controls | Castano et al. - Am J Rhinol Allergy 2009 |
| IL1RL1 | rs1946131 | 102961929 | intronic     | Asthma / Atopy          | 0.015 / 0.050 | Candidate gene study       | French-Canadian founder population | 53 / 42 families | Bossé et al. - Respir Res 2009 |
| IL1RL1 | rs1702706 | 102965332 | intronic     | Total IgE               | 0.02         | Candidate gene study_gene-gene interaction analysis | Dutch 3062 children (birth cohort) | 3062 children (birth cohort) | Reijmerink et al. - Allergy 2010 |
| IL1RL1 | rs1921622 | 102966067 | intronic     | Specific IgE egg 1-2 years | 0.04          | Candidate gene study_gene-gene interaction analysis | Dutch 3062 children (birth cohort) | 3062 children (birth cohort) | Reijmerink et al. - Allergy 2010 |
| IL1RL1 | rs1921622 | 102966067 | intronic     | BHR / asthma / Total IgE | 0.014 / 0.038 / 0.027 | Candidate gene study | Dutch 212 / 193 / 276 families | 212 / 193 / 276 families | Reijmerink et al. - J Allergy Clin Immunol 2008 |
| IL1RL1 | rs10208293| 102966310 | intronic     | Chronic rhinosinusitis | 0.03         | Candidate gene study       | French-Canadian | 206 cases / 196 controls | Castano et al. - Am J Rhinol Allergy 2009 |
| IL1RL1 | rs10208293| 102966310 | intronic     | Specific IgE indoor allergens 6-8 years | 0.03          | Candidate gene study_gene-gene interaction analysis | Dutch 3062 children (birth cohort) | 3062 children (birth cohort) | Reijmerink et al. - Allergy 2010 |
(Table 1). Contd.....

| Gene       | SNP          | Chr. Loc. | SNP Location | Disease/Phenotype          | pValue           | Study                          | Population | N         | Refs.                        |
|------------|--------------|-----------|--------------|---------------------------|-----------------|--------------------------------|------------|-----------|-------------------------------|
| IL1RL1     | rs1861246    | 102966783 | intronic     | BHR / asthma / Total IgE | 0.021 / 0.05 / 0.02 | Candidate gene study Dutch     | 175 / 163 / 230 families |           | Reijmerink *et al.* - J Allergy Clin Immunol 2008 |
| IL1RL1     | rs1861245    | 102966906 | intronic     | Asthma                    | 0.032           | Candidate gene study French-Canadian founder population | 101 families |           | Bossé *et al.* - Respir Res 2009 |
| IL1RL1     | rs4988957    | 102968075 | cod.syn      | Chronic rhinosinusitis    | 0.03            | Candidate gene study French-Canadian | 206 cases / 196 controls |           | Castano *et al.* - Am J Rhinol Allergy 2009 |
| IL1RL1     | rs10204137   | 102968212 | Cod.non.syn  | Chronic rhinosinusitis    | 0.04            | Candidate gene study French-Canadian | 206 cases / 196 controls |           | Castano *et al.* - Am J Rhinol Allergy 2009 |
| IL1RL1     | rs10204137   | 102968212 | Cod.non.syn  | Childhood asthma          | 0.013           | Candidate gene study_follow-up to GWAS Mexican | 492 cases + both parents |           | Wu *et al.* - J Allergy Clin Immunol 2010 |
| IL1RL1     | rs10192157   | 102968356 | Cod.non.syn  | Childhood asthma          | 0.013           | Candidate gene study_follow-up to GWAS Mexican | 492 cases + both parents |           | Wu *et al.* - J Allergy Clin Immunol 2010 |
| IL1RL1     | rs10206753   | 102968362 | Cod.non.syn  | Childhood asthma          | 0.013           | Candidate gene study_follow-up to GWAS Mexican | 492 cases + both parents |           | Wu *et al.* - J Allergy Clin Immunol 2010 |
| IL1RL1 / IL18R1 | rs13015714  | 102971865 | intergenic   | Coeliac disease           | NS              | Candidate gene study_follow-up to GWAS European (Swedish, Norwegian) | 325 families |           | Amundsen *et al.* - Genes Immun 2010 |
| IL1RL1 / IL18R1 | rs12999364  | 102974129 | intergenic   | BHR / asthma              | 0.016 / 0.021   | Candidate gene study Dutch     | 198 / 185 families |           | Reijmerink *et al.* - J Allergy Clin Immunol 2008 |
| IL18R1     | rs2287037 (C-69T) | 102979028 | 5' near-gene | Coal workers' pneumococnosis | NS              | Candidate gene study French     | 200 individuals |           | Nadif *et al.* - Eur Respir J 2006 |
| Gene  | SNP      | Chr. Loc. | SNP Location | Disease/Phenotype       | pValue       | Study                      | Population                      | N    | Refs                                    |
|-------|----------|-----------|--------------|-------------------------|--------------|---------------------------|---------------------------------|------|-----------------------------------------|
| IL18R1| rs2287037| 102979028 | 5' near-gene  | Asthma                 | 0.024        | Candidate gene study      | European (Danish, British, Norwegian) | 736 families | Zhu et al. - Eur J Hum Genet 2008       |
| IL18R1| rs1420099| 102980543 | intronic      | Asthma / Atopic asthma | 0.00069 / 0.0008 | Candidate gene study | European (Danish, British, Norwegian) | 736 families | Zhu et al. - Eur J Hum Genet 2008       |
| IL18R1| rs1420098| 102984279 | intronic      | Asthma                 | 0.037        | Candidate gene study      | European (Danish, British, Norwegian) | 736 families | Zhu et al. - Eur J Hum Genet 2008       |
| IL18R1| rs1362348| 102984624 | intronic      | Asthma / Atopic asthma / BHR | 0.0013 / 0.0024 / 0.048 | Candidate gene study | European (Danish, British, Norwegian) | 736 families | Zhu et al. - Eur J Hum Genet 2008       |
| IL18R1| rs1558627| 102984684 | intronic      | BHR / Total IgE       | 0.049/0.028 | Candidate gene study      | Dutch                           | 180 / 238 families | Reijmer-ink et al. - J Allergy Clin Immunol 2008 |
| IL18R1| rs2058622| 102985424 | intronic      | Atopic asthma         | 0.045        | Candidate gene study      | European (Danish, British, Norwegian) | 736 families | Zhu et al. - Eur J Hum Genet 2008       |
| IL18R1| rs3771170| 102985980 | intronic      | Humoral immunity to Rubella | 0.0003 | Candidate gene study | Somali                           | 89 individuals | Dhiman et al. - Tissue Antigens 2008   |
| IL18R1| rs3771166| 102986222 | intronic      | Childhood asthma      | 0.011        | Candidate gene study, follow-up to GWAS | Mexican                           | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL18R1| rs1974675| 102986375 | intronic      | Asthma / Atopic asthma / BHR | 0.00005 / 0.00001 / 0.036 | Candidate gene study | European (Danish, British, Norwegian) | 736 families | Zhu et al. - Eur J Hum Genet 2008       |
| IL18R1| rs1465321| 102986618 | intronic      | Humoral immunity to Rubella | 0.009 | Candidate gene study | Somali                           | 89 individuals | Dhiman et al. - Tissue Antigens 2008   |
(Table 1). Contd…..

| Gene   | SNP        | Chr. Loc. | SNP Location | Disease/Phenotype                  | pValue  | Study               | Population       | N         | Refs                  |
|--------|------------|-----------|--------------|-----------------------------------|---------|---------------------|------------------|-----------|-----------------------|
| IL18R1 | rs2270297  | 102992675 | intronic     | Humoral immunity to Rubella       | 0.0002  | Candidate gene study | Somali           | 89 individuals | Dhiman et al. - Tissue Antigens 2008 |
| IL18R1 | rs2270297  | 102992675 | intronic     | BHR                               | 0.048   | Candidate gene study | Dutch            | 185 families | Reijmersink et al. - J Allergy Clin Immunol 2008 |
| IL18R1 | rs3213733  | 102997884 | intronic     | Humoral immunity to Rubella       | 0.009   | Candidate gene study | Somali           | 89 individuals | Dhiman et al. - Tissue Antigens 2008 |
| IL18R1 | rs3213733  | 102997884 | intronic     | Asthma                            | 0.0035  | Candidate gene study | Japanese         | 288 cases / 1032 controls | Imada et al. - BMC Res Notes 2009 |
| IL18R1 | rs3213733  | 102997884 | intronic     | Childhood asthma                  | 0.0054  | Candidate gene study | Mexican          | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL18R1 | rs1035130  | 103001402 | cod.syn      | BHR / asthma                       | 0.048 / 0.046 | Candidate gene study | Dutch            | 174 / 159 families | Reijmersink et al. - J Allergy Clin Immunol 2008 |
| IL18R1 | rs3755274  | 103002395 | intronic     | Humoral immunity to Rubella       | 0.009   | Candidate gene study | Somali           | 89 individuals | Dhiman et al. - Tissue Antigens 2008 |
| IL18R1 | rs2241117  | 103003043 | intronic     | Humoral immunity to Rubella       | 0.001   | Candidate gene study | Somali           | 89 individuals | Dhiman et al. - Tissue Antigens 2008 |
| IL18R1 | rs3771161  | 103003961 | intronic     | Humoral immunity to Rubella       | 0.009   | Candidate gene study | Somali           | 89 individuals | Dhiman et al. - Tissue Antigens 2008 |
| IL18R1 | rs4851004  | 103009537 | intronic     | Childhood asthma                  | 0.0079  | Candidate gene study | Mexican          | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |

| Gene     | SNP      | Chr. Loc. | SNP Location | Disease/Phenotype            | pValue     | Study                      | Population                  | N                  | Refs.                          |
|----------|----------|-----------|--------------|-----------------------------|------------|----------------------------|-----------------------------|-----------------------|--------------------------------|
| IL18R1   | rs2287033| 103011237 | intronic     | Childhood asthma            | 0.0063     | Candidate gene study, follow-up to GWAS | Mexican                    | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL18R1   | rs3732127| 103013750 | 3' UTR       | Humoral immunity to Rubella | 0.009      | Candidate gene study        | Somali                     | 89 individuals         | Dhiman et al. - Tissue Antigens 2008 |
| IL18R1   | rs1420094| 103015687 | 3' UTR       | Childhood asthma            | 0.0063     | Candidate gene study, follow-up to GWAS | Mexican                    | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL18R1   | rs1420094| 103015687 | 3' UTR       | Atopic asthma               | 0.0063     | Candidate gene study        | European (Danish, British, Norwegian) | 736 families       | Zhu et al. - Eur J Hum Genet 2008 |
| IL18R1 / IL18RAP | rs1035127| 103019919 | intergenic   | Crohn's disease             | 1.2 x 10^{-7} | GWAS                      | Caucasian (American, Canadian, Belgian, French, British) | 2325 cases / 1809 controls + 1339 families | Barrett et al. - Nat Genet 2008 |
| IL18RAP  | rs1420106| 103035044 | 5' near-gene | BHR / Total IgE             | 0.023 / 0.012 | Candidate gene study        | Dutch                      | 184 / 234 families     | Videman et al. - Arthritis Rheum 2009 |
| IL18RAP  | rs1420100| 103037002 | intronic     | Lumbar disc signal intensity | 0.005     | Candidate gene study        | Finnish                    | 588 individuals        | Shirts et al. - Am J Med Genet B Neuro-psychiatr Genet 2008 |
| IL18RAP  | rs2272127| 103039873 | intronic     | Schizophrenia+Herpes seropositivity | 0.03     | Candidate gene study        | Caucasian (American)        | 478 cases / 501 controls | Hunt et al. - Nat Genet 2008 |
| IL18RAP  | rs917997 | 103070568 | intergenic   | Coeliac disease             | 8.49 x 10^{-10} | Candidate gene study, follow-up to GWAS | Northern European          | 767 cases / 1422 controls | Hunt et al. - Nat Genet 2008 |
(Table 1). Contd…..

| Gene       | SNP         | Chr. Loc. | SNP Location | Disease/Phenotype | pValue     | Study                  | Population                      | N                  | Refs.                        |
|------------|-------------|-----------|--------------|-------------------|------------|------------------------|---------------------------------|--------------------|-------------------------------|
| IL18RAP    | rs917997    | 103070568 | intergenic   | Type 1 diabetes   | 8.03 x 10^{-5} | Candidate gene study   | Caucasian (Irish, British, American, Romanian, Danish, Norwegian, Finnish) | 8064 cases / 9339 controls | Smyth et al. - N Engl J Med 2008 |
| IL18RAP    | rs917997    | 103070568 | intergenic   | Crohn's disease   | 2.2 x 10^{-6}  | Candidate gene study   | European                        | 1689 cases / 1936 controls | Wang et al. - Hum Genet 2010 |
| Chr 2      |             |           |              | Type 2 diabetes   | LOD=4.53     | Genetic linkage study  | African-American                | 580 families               | Elbein et al. - Diabetes 2009  |
| IL18RAP    | 6 Tag SNPs  |           |              | Cardiovascular disease | NS         | Candidate gene study   | European                        | 1416 cases / 1772 Controls | Grisoni et al. - BMC Med Genet 2009 |
| IL18R1     | 5 Tag SNPs  |           |              | Cardiovascular disease | NS         | Candidate gene study   | European                        | 1416 cases / 1772 Controls | Grisoni et al. - BMC Med Genet 2009 |
| IL1RL1 / IL18R1 | Haplo: rs1026753/rs12999364/rs1420099 | -          |              | BHR               | 0.006      | Candidate gene study   | Dutch                           | 179 families               | Reijmer-ink et al. - J Allergy Clin Immunol 2008 |
| IL18R1     | Haplo:rs1420099/rs1558627/rs2270297 | -          |              | Asthma             | 0.002      | Candidate gene study   | Dutch                           | 180 families               | Reijmer-ink et al. - J Allergy Clin Immunol 2008 |
| IL1RL1     | Haplo:rs1921622/rs1861246/rs10206753 | -          |              | BHR / asthma / Total IgE | 0.0009 / 0.0008 / 0.007 | Candidate gene study   | Dutch                           | 192 / 170 / 245 families | Reijmer-ink et al. - J Allergy Clin Immunol 2008 |
IL1RL1: functional characterization of genetically-associated variants is necessary to determine the causal pathways leading to expression and/or function changes in the proteins.

As shown by numerous animal model studies, targeting the IL1RL1/IL33 axis is potentially a very promising therapeutic avenue for lung, heart and other immune and inflammatory disorders. In order to move the field forward, it will be important to investigate genetic association of the IL1RL1 region (including the surrounding genes) in different populations with different LD patterns; this will permit a better understanding of the biology behind this region’s involvement in immune and inflammatory disorders and thus facilitate and focus future therapeutic targeting efforts.

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**Table 1.** Contd…..

| Gene     | SNP       | Chr. Loc. | SNP Location | Disease/Phenotype | pValue | Study                  | Population | N         | Refs.         |
|----------|-----------|-----------|--------------|-------------------|--------|------------------------|------------|-----------|---------------|
| IL18R1 / | IL18RAP   | 22 candidate SNPs | -            | -                 | -      | Candidate gene study    | German      | 142 cases / 114 controls | Tret et al. - Circulation 2005 |
| IL1RL1   | multimarker (11) | -          | -            | -                 | -      | Candidate gene study_follow-up to GWAS | Mexican     | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |
| IL18R1   | multimarker (9) | -          | -            | -                 | -      | Candidate gene study_follow-up to GWAS | Mexican     | 492 cases + both parents | Wu et al. - J Allergy Clin Immunol 2010 |

**Abbreviations**

- IBID: Inflammatory bowel disease
- BHR: Bronchial hyper-responsiveness
- GWAS: Genome-wide association study
- Chr.Loc: Chromosomal location based on NCBI build 37.1
- Chr 2: Chromosome 2
- Haplo: Haplotype
- NS: Non significant
- Cod non.syn: Coding non synonymous SNP
- Cod.syn: Coding synonymous SNP

Same SNPs are hilighted with the same color; different colors are merely for ease of viewing, and are inconsequential.
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