

## REVIEW

# Current concepts of IgE regulation and impact of genetic determinants

D. P. Potaczek and M. Kabesch

Department of Pediatric Pneumology, Allergy and Neonatology, Hannover Medical School, Hannover, Germany

## Clinical & Experimental Allergy

### Correspondence:

Michael Kabesch, Department of Pediatric Pneumology, Allergy and Neonatology, Hannover Medical School, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany.

E-mail: kabesch.michael@mh-hannover.de

mh-hannover.de

Cite this as: D. P. Potaczek and M. Kabesch, *Clinical & Experimental Allergy*, 2012 (42), 852–871.

### Summary

Immunoglobulin E (IgE) mediated immune responses seem to be directed against parasites and neoplasms, but are best known for their involvement in allergies. The IgE network is tightly controlled at different levels as outlined in this review. Genetic determinants were suspected to influence IgE regulation and IgE levels considerably for many years. Linkage and candidate gene studies suggested a number of loci and genes to correlate with total serum IgE levels, and recently genome-wide association studies (GWAS) provided the power to identify genetic determinants for total serum IgE levels: 1q23 (*FCER1A*), 5q31 (*RAD50*, *IL13*, *IL4*), 12q13 (*STAT6*), 6p21.3 (*HLA-DRB1*) and 16p12 (*IL4R*, *IL21R*). In this review, we analyse the potential role of these GWAS hits in the IgE network and suggest mechanisms of how genes and genetic variants in these loci may influence IgE regulation.

**Keywords** asthma, genome-wide association study, immunoglobulin E (IgE), polymorphism

*Submitted 04 August 2011; revised 21 November 2011; accepted 09 December 2011*

### Introduction

Immunoglobulin E (IgE) is the class of human antibodies that is most frequently recognized for its role in type I hypersensitivity (allergic) reaction [1–3]. In predisposed, atopic individuals, IgE is produced against specific common environmental antigens (allergens) [4]. In a type I hypersensitivity reaction, allergens cross-link IgE molecules and bind the high-affinity IgE receptor (FcεRI) on the surface of basophils or mast cells, which results in the release of local mediators, such as histamine [3, 5]. This leads to local allergic symptoms most frequently from the lower or upper respiratory tract, skin, gut or eyes [2, 6], but may also turn into a systemic, life threatening immune reaction: the anaphylactic shock [2, 7].

In this review, we briefly describe the structural and functional components of the IgE network and focus on regulation of IgE by genetic determinants. We specifically address genes identified by GWAS approaches in more detail and show how genes and polymorphisms associated with total serum IgE levels may influence the IgE network and mechanisms of IgE regulation.

### Biological role of IgE

Among the five major classes of human antibodies, IgE deserves special attention. IgE and IgG are the two

immunoglobulins exclusively present in mammals [3, 8]. It is thought that IgE and IgG appeared early in mammalian evolution by duplication of an ancestral immunoglobulin Y (IgY) gene [8–10], the major antibody of non-mammalian vertebrates, amphibians, birds and probably reptiles [10]. IgG retained the function of a major serum antibody, whereas IgE specifically activates mast cells and basophils [8, 9]. The separation of IgG- (opsonic) and IgE-mediated (anaphylactic) activities of IgY may have allowed for a more specific regulation of both immune mechanisms [11, 12]. IgE turnover [3, 5, 6, 13] and IgE responses [11, 12] are under tight control, keeping serum IgE levels very low. In addition, the fact that IgE and its dependent anaphylactic mechanisms were not abandoned during the evolution of mammals suggests that the presence of this unique isotype may be necessary or at least beneficial [8].

It has long been suggested that the primary biological role of IgE is to provide immunity against multicellular parasites [13]. However, with the exception of *Trichinella spiralis* [14] and *Schistosoma mansoni* [15, 16], there is only little evidence for a significant function of IgE in the defence against parasitic worms [17]. Helminth infections tend to induce large amounts of polyclonal IgE, not specific against parasites [17]. This may have led to the assumption that helminthic

infestations protect against the development of atopic disorders and/or reduce their severity [18, 19]. Recent results suggest that IgE also plays a role in host defence against protozoa such as *Toxoplasma gondii* [20]. The role of IgE in helminthic infection [17] and the relationship between intestinal parasite infestation and atopic diseases [19] are reviewed elsewhere in more detail.

Epidemiological and experimental data suggest that IgE may also contribute to anti-tumour immune responses [21, 22], as recently reviewed [12]. IgE antibodies that recognize antigen-rich intact tumour cells interact with immune cells expressing IgE receptors, thereby recruiting effector cells mediating oncolytic activity [12, 23]. Both the high-affinity (Fc $\epsilon$ RI) and the low-affinity (Fc $\epsilon$ RII) IgE receptors seem to be involved [12, 21, 24, 25]. Genetic variants in Fc $\epsilon$ RI were reported to be associated with breast cancer [26], and variants in Fc $\epsilon$ RII with lung cancer [27].

### The IgE network

The term 'IgE network' was first introduced and developed by Sutton & Gould [5, 28]. It relates to IgE, principal and secondary IgE receptors and further biomolecules associated with the activity and control of IgE (Fig. 1).

### IgE

IgE is composed of two identical heavy chains and two identical light chains. The light chain comprises one variable region and one constant domain. The heavy chain contains two regions, one variable and one constant region. The constant region includes four domains [5, 6, 29]. Immunoglobulin light chains are encoded on chromosome 2p11 ( $\kappa$ ) or 22q11 ( $\lambda$ ); the heavy chain on 14q32 [6, 30, 31]. Variable regions of light and heavy chains create two identical antigen-binding sites. Such structure corresponds to secretory IgE [5, 6, 29]. The membrane-bound form of IgE (mIgE) displays the same basic structure, but an extracellular membrane proximal domain (EMPD), a transmembrane sequence and a cytoplasmic tail is added to the last constant domain of the heavy chain [32–35]. IgE EMPD exists as at least two isoforms of different length [32–35].

Surface forms of immunoglobulins associate with two membrane proteins, Ig $\alpha$  (CD79a) and Ig $\beta$  (CD79b), to form the B-cell antigen receptor (BCR) that plays an important role in survival and development of the B cell at any stage [11, 29, 33, 36–38]. Interestingly, synthesis of mIgE seems to be more difficult than the production of membrane-bound forms of other immunoglobulin isotypes (excluding mIgE) and the synthesis of secretory forms of antibodies (including secretory IgE). While usually the polyadenylation signal

during mRNA maturation is a conservative and optimal AATAAA motif, mIgE is polyadenylated at three potential alternative sites, AGTAAA, AAGAAA and ATAAAA [5, 11, 33, 35, 36]. This results in a lower rate of matured mRNA production and diminished stability, and in turn in lower mIgE-based BCR representation and death of IgE producing clones.

Like other classes of immunoglobulins, IgE is exclusively produced by B cells and plasma cells. Two steps of somatic DNA rearrangements are required for IgE expression. The first rearrangement during B-cell development is called 'V(D)J' recombination. Genes for immunoglobulin heavy chains (IgH) are composed of numerous V (variable), D (diversity) and J (joining) segments encoding for different antigen-binding regions [6, 39–41]. Recombination allows for the synthesis of antibodies against a wide spectrum of potential antigens. Similarly, the genes encoding immunoglobulin light chain genes ( $\kappa$  and  $\lambda$ ) have multiple V and J segments [6, 40]. Naïve mature B cells are capable of producing immunoglobulin M (IgM) or D (IgD), the latter through differential splicing of the precursor mRNA containing both constant (C) regions, C $\mu$  and C $\delta$  respectively [6, 42]. Following antigen activation and an appropriate stimulation, mature B cells undergo the second somatic rearrangement step that involves only the chromosomal IgH locus, and is called 'class-switch recombination' (CSR) or simply 'class switching' [6, 40, 43–45]. In addition to V, D and J segments and C regions for IgM (C $\mu$ ) and IgD (C $\delta$ ), the human IgH chromosomal locus has several further alternative segments encoding the C region (C $\gamma$ 3, C $\gamma$ 1, C $\alpha$ 1, C $\gamma$ 2, C $\gamma$ 4, C $\epsilon$  and C $\alpha$ 2) (Fig. 2), which enables production of antibodies belonging to different functional classes upon CSR (IgG3, IgG1, IgA1, IgG2, IgG4, IgE and IgA2 respectively) [6, 40, 42]. With the exception of C $\delta$ , every C region is preceded by 'intervening' (I) and 'switch' (S) regions (Fig. 2) [6, 40, 42].

CSR is initiated by activation-induced cytidine deaminase (AID), which deaminates dC residues in both genomic strands of two transcriptionally active S regions [46–51]. This leads to double-strand DNA breakage in both S regions and, subsequently, formation of an S–S synapse and an intervening loop [45, 46, 50–52]. Next, somatic recombination occurs, which involves DNA repair mechanisms for re-ligation that results in the deletion of S–S intervening loop. A chromosomal IgH locus lacking S–S intervening region is then ready to express mature IgH [45, 46, 50–52]. The loop itself is excised in the form of a so-called 'switch circle', expressing the switch circle transcript, a specific marker for ongoing CSR [6, 52, 53]. Molecular mechanism of CSR (exemplified by direct CSR from IgM to IgE) is presented in Fig. 2. In direct CSR from IgM to IgE, deletional recombination between S $\mu$  and S $\epsilon$

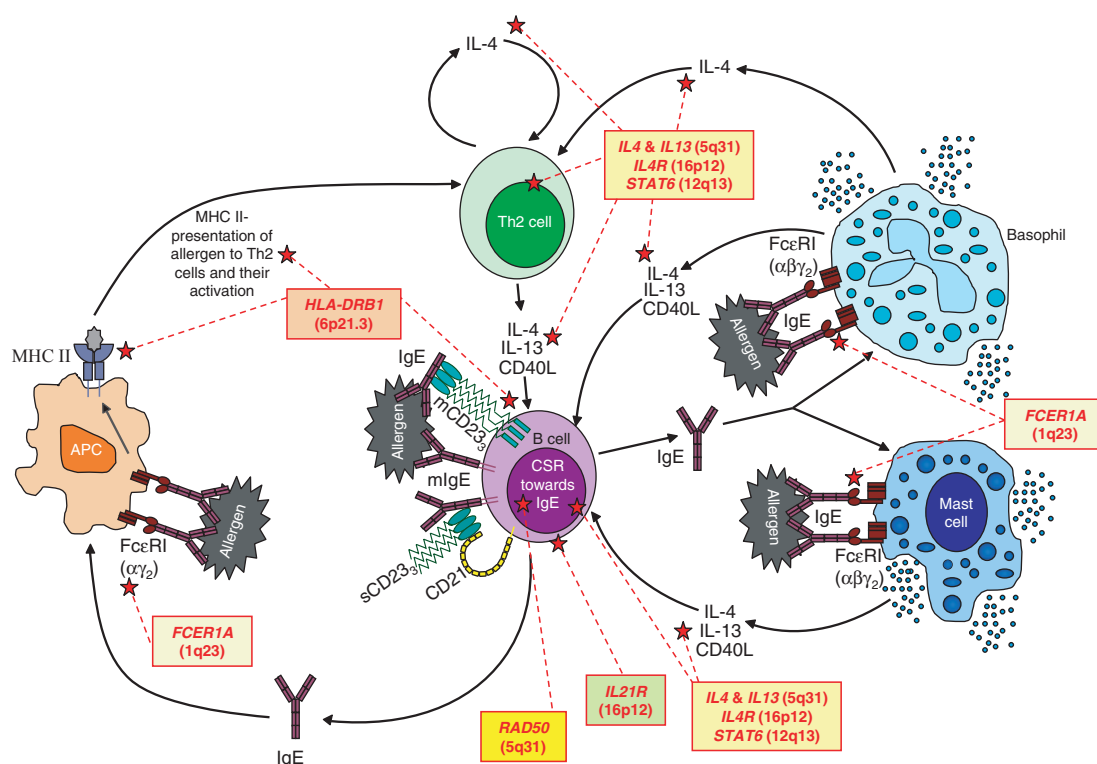


Fig. 1. Basic molecules and cells contributing to the IgE network, IgE function and IgE regulation. Gene products identified by GWA studies on total serum IgE are depicted in red (with chromosomal loci provided). IL-4 denotes interleukin-4; MHC II, major histocompatibility complex, class II; APC, antigen-presenting cell; IL-13, interleukin-13; CD40L, CD40 ligand; mIgE, membrane IgE; FcεRI, the high-affinity IgE receptor; CSR, class-switch recombination; (m/s) CD23, (membrane/soluble) low-affinity IgE receptor, trimeric form. The figure was adopted and modified from Gould & Sutton [5] and further inspired by graphics from other sources [87, 118, 125].

regions occurs. After excision of S $\mu$ -S $\epsilon$  loop, the IgH locus is ready to express the IgE heavy chain (Fig. 2) [6, 42, 52]. In addition to direct CSR from IgM to IgE, IgM can also switch to IgE in a sequential manner *via* IgG. In the first step of CSR from IgM to IgG, deletional recombination between S $\mu$  and S $\gamma$  happens that enables synthesis of IgG [52, 54]. In the second step of CSR from IgG to IgE, deletional recombination occurs between S $\mu$ /S $\gamma$  and S $\epsilon$  with subsequent formation of IgH locus expressing IgE. This kind of CSR to IgE is feasible for IgG1, IgG3 and IgG4, whereas IgG2 is not able to switch to IgE [52, 54].

CSR towards IgE is under tight control. Several steps are absolutely necessary for a B cell to undergo IgE CSR [3, 6, 55–57]. A first signal for CSR is provided by interleukin-4 (IL-4) and interleukin-13 (IL-13) [3, 6, 55, 57, 58] which act through shared pathway components (Figs 1 and 2). There are two basic types of IL-4 receptor (IL-4R). Type I IL-4R is a dimer composed of IL-4R $\alpha$  subunit (IL-4R $\alpha$ ) and a so-called 'common  $\gamma$ -chain' ( $\gamma$ c), a subunit common for several interleukin receptors (Fig. 2). This receptor type is specific for IL-4. Type II IL-4R, also called 'IL-13 receptor' (IL-13R), comprises IL-4R $\alpha$  and IL-13 receptor  $\alpha$ 1-subunit (IL-13R $\alpha$ 1). This

type of IL-4R can be activated by both IL-4 and IL-13 [57, 59, 60] (Fig. 2). Stimulation of both types of receptors results in activation of Janus kinases (JAK1, JAK2, JAK3, TYK1 and TYK2), which leads to phosphorylation, dimerization and nuclear migration of signal transducer and activation of transcription 6 (STAT6) transcription factor [3, 6, 57–62] (Fig. 2). The second signal for CSR towards IgE is provided by an interaction between B-cell surface CD40 and its ligand, CD40L [3, 6, 55, 57, 58] (Figs 1 and 2). Activated CD40 recruits tumour-necrosis factor receptor-associated factors (TRAFs) inducing nuclear translocation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) [3, 57, 62–65]. STAT6 and NF- $\kappa$ B interact with their respective responsive DNA elements in the  $\epsilon$  germline gene promoter, located just upstream of I $\epsilon$  region [6, 57, 66, 67]. This leads to  $\epsilon$  germline gene transcription with subsequent splicing to a 'sterile' transcript (Fig. 2). The term 'sterile' refers to the fact that the I $\epsilon$  exon contains stop codons in all three possible frames, making it impossible to express any immunoglobulin [50, 55]. Additional transcription factors involved in positive regulation of human  $\epsilon$  germline gene promoter are CCAAT/enhancer binding protein (C/EBP), PU.1 and B-cell-specific activator protein (BSAP;

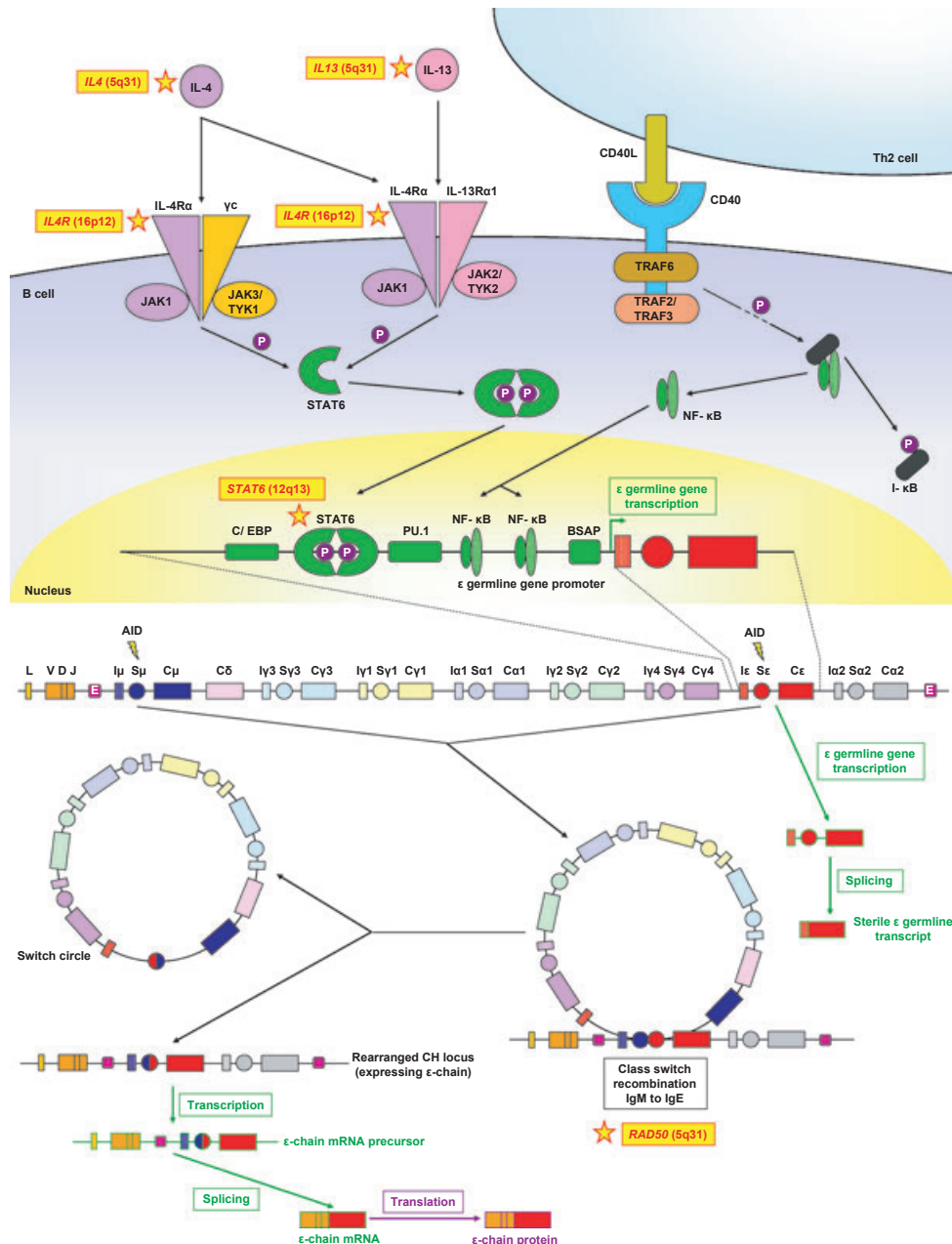


Fig. 2. Induction of  $\epsilon$  germline gene transcription in human (upper panel). Organization of human immunoglobulin heavy chain (IgH) locus (chromosome 14q32) after V(D)J recombination and a mechanism of direct class-switch recombination (CSR) from IgM to IgE (lower panel). Stimulation of B cell by interleukin-4 (IL-4) and/or interleukin-13 (IL-13) leads to phosphorylation, dimerization and nuclear migration of signal transducer and activation of transcription 6 (STAT6) factor. Signalling through CD40L/CD40 unblocks nuclear factor- $\kappa$ B (NF- $\kappa$ B), which subsequently migrates to the nucleus. STAT6 and NF- $\kappa$ B induce  $\epsilon$  germline gene transcription. Other transcription factors also contribute to activation of  $\epsilon$  germline gene transcription, including CCAAT/enhancer binding protein (C/EBP), PU.1 transcription factor and B-cell-specific activator protein (BSAP; paired box protein 5, PAX5). Transcription of  $\epsilon$  germline gene, comprising its intervening (I $\epsilon$ ), switch (S $\epsilon$ ) and constant (C $\epsilon$ ) regions, is a prerequisite for CSR towards IgE to happen. Deletional recombination between S $\mu$  and S $\epsilon$  is initiated by an activation-induced cytidine deaminase (AID). Chromosomal region between S $\mu$  and S $\epsilon$  forms a loop. DNA breaks are repaired, finally leading to the formation of switch circle (from a loop) and rearranged immunoglobulin locus. Now, IgE can be produced. For more details, please, refer to the main document. Human IgH locus is shown without pseudo-( $\psi$ )-genes. The size of the DNA fragments and the distances between them do not reflect real chromosomal relationships. The upper panel of figure has been adopted and modified from Geha et al. [57] and Hellman [3] with further inspiration by graphics from the other sources [6, 42–44, 58, 59, 62, 65, 71]. The lower panel of the figure has been adopted and modified from Kinoshita & Honjo [41], Gould et al. [6, 42, 46], Stavnezer [44, 51], Stavnezer et al. [50], Takhar et al. [52], Kracker & Durandy [45], Bacharier et al. [40], Chaudhuri & Alt [47] and Martin & Scharff [48]. Products of the genes identified by GWA studies on total serum IgE potentially involved in the stimulation and molecular mechanisms of CSR towards IgE are depicted with stars.

paired box protein 5, PAX5) [6, 42, 58, 66–68]. Moreover, Myb factors have been shown to inhibit STAT6-dependent activation of  $\epsilon$  germline gene promoter in humans [6, 69]. In mice, the activation factors are similar [43, 70, 71], but a contribution of AP1 and E2A transcription factors has been shown [43, 72, 73]. In addition, Bcl6 and Id2 factors are important negative regulators of  $\epsilon$  germline gene expression in mice [43, 71, 72].

Although it is generally thought that the expression of the  $\epsilon$  germline gene is a prerequisite of CSR towards IgE [3, 42–44, 57], the exact function of germline 'IgH' gene transcription/transcripts is still under extensive debate [42, 44, 55, 74–76]. Germline transcription may create short regions of single-stranded DNA, which are the substrate for AID. Furthermore, germline transcription may recruit AID and could alter histone modification in a manner favouring its accessibility for AID [47, 50, 51]. Transcription of AID itself is also co-stimulated by IL-4/IL-13-induced STAT6 and CD40L/CD40-activated NF- $\kappa$ B through their binding sites in AID promoter [3, 57]. However, the regulation of AID expression seems to be far more complex [45, 51, 77]. AID also plays a crucial role in another process of somatic changes in the IgH locus, the somatic hypermutation (SHM) [41, 48, 49, 78]. During SHM, genes encoding variable regions of heavy and light chains accumulate massive point mutations which, in addition to V(D)J recombination, further increases their variability and antigen-binding spectrum [48, 49, 78]. More details on somatic DNA changes involved in V(D)J recombination [39, 41] or SHM [41, 49], the role of AID in SHM and CSR [41, 45, 47, 48, 78], the molecular mechanisms of CSR [6, 40–42, 45, 47, 49–51] and the regulation of CSR towards IgE [3, 6, 42, 43, 50, 57, 58], can be found elsewhere.

The signals required for CSR towards IgE include IL-4/IL-13 and CD40L to cross-link B-cell CD40 [3, 5, 40, 42, 57]. They are provided by T-helper type 2 (Th2) lymphocytes (major source), basophils, mast cells, B cells or  $\gamma\delta$ T cells [79–82] (Fig. 1). In addition, it seems that basophils are potent inducers of Th2 cells [82–88], although this notable aspect of basophil biology is still debated [89, 90].

Plasma half-life of human IgE (2.5 days) is very short compared with other immunoglobulin classes, especially IgG (21 days) [3]. Such a short plasma half-life may be considered as another mechanism controlling serum IgE levels [11, 12, 33]. Indeed, serum IgE levels are about  $10^4$  times lower than IgG concentrations in healthy individuals [3, 5]. There is growing evidence that the synthesis of IgE may not only take place in germinal-centres of lymph nodes but also in local mucosal tissues [3, 5, 46]. CSR towards IgE and local IgE production were observed in nasal mucosa in allergic rhinitis (AR)

and bronchial mucosa in asthma [52, 91, 92]. In asthmatics, this was not restricted to atopic patients [53]. In addition, local CSR to IgE and IgE production were recently reported in oesophageal mucosa of patients suffering from eosinophilic oesophagitis [93]. Mechanisms of local IgE synthesis are discussed in more details elsewhere [46].

In models of local IgE production, it has been shown that IgE against a single specific allergen can account for up to 50% of total IgE content [5, 94]. Correlations between specific and total serum IgE have been observed to a lesser extent in blood [95–98]. Specific serum IgE against certain allergen can account for up to 20–25% of total serum IgE, driving the overall value of total blood serum IgE [97]. Geographic (or ethnic) differences in sensitization to specific allergens exist [95–97].

### IgE receptors

Fc $\epsilon$ RI and Fc $\epsilon$ RII are the two main receptors for IgE. They differ in structure, function and location [99, 100]. Several other molecules can be considered as additional IgE receptors or co-receptors, like galectin-3, some integrins or CD21 [5, 100–104]. Galectin-3 can interact with IgE and/or Fc $\epsilon$ RI on the surface of basophils or mast cells. CD21 is an important co-receptor of Fc $\epsilon$ RII involved in IgE regulation [5, 100, 101].

Human Fc $\epsilon$ RI is composed of up to four protein chains of three kinds:  $\alpha$ - (Fc $\epsilon$ RI $\alpha$ ),  $\beta$ - (Fc $\epsilon$ RI $\beta$ ) and  $\gamma$ -subunit (Fc $\epsilon$ RI $\gamma$ ), encoded by *FCER1A*, *FCER1B* or *FCER1G*, respectively [1, 100, 105]. Of the three Fc $\epsilon$ RI subunits, only Fc $\epsilon$ RI $\alpha$  is IgE receptor-specific, whereas Fc $\epsilon$ RI $\beta$  and Fc $\epsilon$ RI $\gamma$  are also a part of other Fc receptors. For example, Fc $\epsilon$ RI $\gamma$  associates with Fc $\gamma$ RI, Fc $\gamma$ RIII and Fc $\alpha$ RI depending on cellular context, whereas in mast cells, Fc $\epsilon$ RI $\beta$  is shared with Fc $\gamma$ RIII [1, 2, 105]. On mast cells and basophils, Fc $\epsilon$ RI has a tetrameric structure comprising one  $\alpha$ -, one  $\beta$ - and two  $\gamma$ -subunits ( $\alpha\beta\gamma_2$ ) [1, 2, 106]. On the surface of antigen-presenting cells (APCs), including monocytes, macrophages, dendritic cells (DCs) and Langerhans cells, and also on platelets, smooth muscle cells or eosinophils (and potentially other cell types), human Fc $\epsilon$ RI is expressed in a trimeric form, lacking the  $\beta$ -subunit ( $\alpha\gamma_2$ ) [2, 107–109]. Fc $\epsilon$ RI $\alpha$  is a member of the immunoglobulin superfamily and comprises two extracellular immunoglobulin-like domains, a hydrophobic transmembrane region and a short cytoplasmic tail. Fc $\epsilon$ RI $\alpha$  is a subunit responsible for binding of IgE molecule [110, 111]. Fc $\epsilon$ RI $\beta$  has four transmembrane regions and two cytoplasmic tails. Fc $\epsilon$ RI $\gamma$  consists of a transmembrane region and a cytoplasmic tail. Fc $\epsilon$ RI $\beta$  and Fc $\epsilon$ RI $\gamma$  both contain an immunoreceptor tyrosin-based activator motif (ITAM). The  $\beta\gamma_2$  or  $\gamma_2$  complex is the Fc $\epsilon$ RI signalling module.

Phosphorylation of their ITAM motifs upon receptor stimulation is crucial for the signal transduction. In contrast to FcεRIγ, the ITAM motif in FcεRIβ is not directly involved in downstream signalling, but functions as a signal amplifier [112, 113]. Cross-linking of IgE molecules occupying FcεRI on mast cells and basophils leads to activation of the receptor and the subsequent signal transduction. In turn, effector cells degranulate and release local mediators, such as histamine [3, 5, 114]. FcεRI expressed on the surface of APCs also contributes to antigen presentation [115, 116]. Antigen-IgE-FcεRI complexes are transported from the APC surface to the intracellular antigen-presenting compartment and delivered to the major histocompatibility complex (MHC) class II antigen-presentation pathway [100, 101, 105]. FcεRIα can also exist in a soluble form (sFcεRIα) [117], as very recently reviewed [104].

FcεRII substantially differs in structure from FcεRI (FcεRIα), and almost all other Fc receptors belonging to the immunoglobulin superfamily [100, 118]. The type II transmembrane protein FcεRII consists of the CD23 polypeptide only. In the CD23 polypeptide, a calcium-dependent C-terminal globular extracellular domain of C-lectin type is followed by a stalk region with few repeats serving as a putative leucine zipper required for oligomerization of CD23 polypeptides [6, 118, 119]. In addition, a short C-terminal tail also extends from C-terminal globular extracellular domain of C-lectin type [5, 6]. The stalk region is followed by a sole hydrophobic transmembrane region and a short N-terminal cytoplasmic tail [5, 6, 119]. The stalk region is susceptible to proteolysis [5, 118]. The gene encoding for the CD23 polypeptide is *FCER2* [118, 120]. *FCER2* possesses two alternative transcription start sites driving synthesis of two mRNA variants which leads to synthesis of two CD23 polypeptides differing in the first seven (CD23a) or six (CD23b) amino acids of the N-terminal cytoplasmic tail [120–123]. CD23a is exclusively expressed by B cells in a constitutive manner, whereas CD23b can be induced by IL-4 on the surface of monocytes/macrophages, B cells, T cells, eosinophils, DCs and epithelial cells [5, 100, 118, 120].

FcεRII is called 'low-affinity IgE receptor' which suggests that its affinity for IgE is much lower than that of the 'high-affinity IgE receptor' FcεRI ( $K_a \approx 10^{10}$ – $10^{11}$  M<sup>-1</sup>). Indeed, IgE-binding affinity of a single CD23 polypeptide is low ( $K_a \approx 10^6$ – $10^7$  M<sup>-1</sup>), but substantially increased in its trimeric form ( $K_a \approx 10^8$ – $10^9$  M<sup>-1</sup>) [5, 124]. The membrane-bound form of CD23 is trimeric, but can be cleaved at the site of the proteolysis susceptible stalk region. This may lead to a formation of soluble CD23 fragments (sCD23) whose activity depends on oligomerization status. A disintegrin and metalloproteinase 10 (ADAM10) is considered the pri-

mary cleaving enzyme generating smaller sCD23 fragments [5, 118, 125, 126]. Interactions of various forms of CD23 with its ligands CD21 and IgE on the B-cell surface underlie a pivotal mechanism of IgE homeostasis in humans [5, 118, 123, 125, 126]. Cross-linking of membrane-bound CD23 and mIgE by an allergen-serum IgE complex results in suppression of IgE synthesis. In contrast, cross-linking of mIgE and CD21 by trimeric sCD23 leads to enhanced IgE production [5, 125]. This mechanism can be supplemented by the effects of monomeric sCD23 that competes with trimeric CD23 for a binding to CD21 and mIgE, which prevents cross-linking of CD21 and mIgE by trimeric sCD23 and related up-regulation of IgE synthesis [104, 126]. Monomeric sCD23 lacking a CD21 binding site may also lower IgE levels by disruption of co-ligation between membrane CD21 and mIgE by trimeric sCD23 [127]. For mice, it was recently suggested that binding of IgE to CD23 expressed on B cells, rather than to FcεRI present on basophils or mast cells, regulates a pool of free serum IgE [128]. B-cell membrane-bound CD23 also enhances IgE-dependent antigen presentation to T cells [5, 129, 130]. Similar to FcεRI in APCs [100, 101, 105], antigen-IgE-CD23 complexes are transported from the B-cell surface to endosomal network compartments where processing by proteolytic enzymes and loading onto MHC class II antigens takes place [5, 131, 132].

### Genetic variants and serum IgE levels

Although IgE synthesis and serum levels are tightly controlled by mechanisms described above, serum IgE concentrations can be affected by various influences including age, gender, ethnicity, smoking status and genetics [133–137]. Heritability of total serum IgE levels is estimated to be up to 80% and even stronger for cord blood IgE concentrations [138–141]. Genetic influences on serum IgE were suspected in the early days of allergy genetics, and a polygenic pattern of inheritance on the population level was suggested [136, 142–144].

Monogenic disorders such as hyper-IgE syndrome (HIES) can lead to excessive IgE production and very high serum levels [43, 145–147]. HIES can be inherited in an autosomal dominant and an autosomal recessive way. However, its sporadic form is most prevalent [148, 149]. Dominant negative mutations in *STAT3* (encoding signal transducer and activation of transcription 3 – STAT3) have been detected in autosomal dominant and sporadic HIES [43, 147, 150, 151], whereas mutations of *TYK2* or *DOCK8* have been observed in its autosomal recessive form [43, 145, 152, 153]. Interestingly, *STAT3* genetic variants detected in HIES were neither associated with total or specific serum IgE levels nor asthma, AR or AD in the general population [154]. Other mono-

genic disorders associated with highly elevated serum IgE levels include Omenn syndrome, Wiskott–Aldrich syndrome, adenosine deaminase (ADA) deficiency and IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) [145, 146, 155]. Of note, IPEX is caused by defects in regulatory T cells (Treg), resulting from null mutations in the forkhead box protein 3 (FOXP3) gene (*FOXP3*) [43, 155]. Interestingly, an association between single-nucleotide polymorphisms (SNPs) within the *FOXP3* locus and AR has been reported by three independent groups [156–158].

### Chromosomal loci and genes identified to influence total serum IgE levels by linkage and candidate gene studies

To identify loci and genes underlying total serum IgE levels detected by linkage and candidate gene approaches, we conducted a systematic literature search. Using the phrase '(SNP OR polymorphism OR linkage) AND (serum OR total) AND (IgE OR immunoglobulin E)' to search the PubMed database [159] (10 July 2011), we retrieved 712 abstracts. After initial screening, we identified 223 manuscripts of potential interest, which were individually analysed for reports of linkage and/or association with total serum IgE. Chromosomal regions showing linkage with total serum IgE levels are presented in Fig. 3. Genes in which polymorphisms were associated with total serum IgE in at least three independent studies are given in Fig. 4.

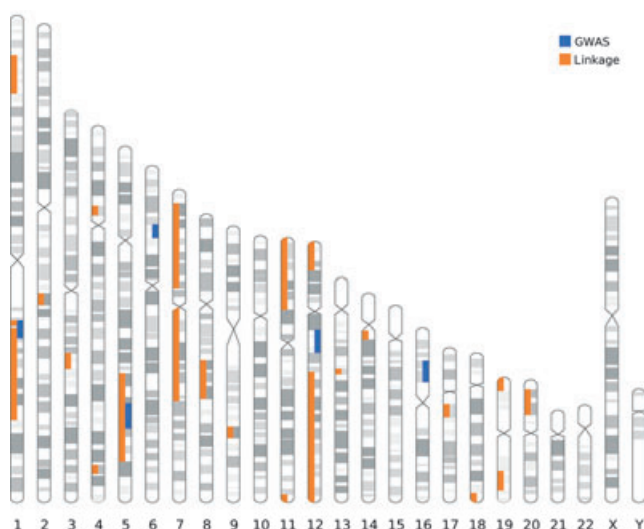


Fig. 3. Loci identified to be associated with total serum IgE levels in genome-wide association (in blue) and linkage (in orange) studies. Only linkage studies with more than five hundred genotyped participants were included. References underlying the figure can be found in Appendix S1. The figure was generated using Idiographica v. 2.0 online software [280, 281].

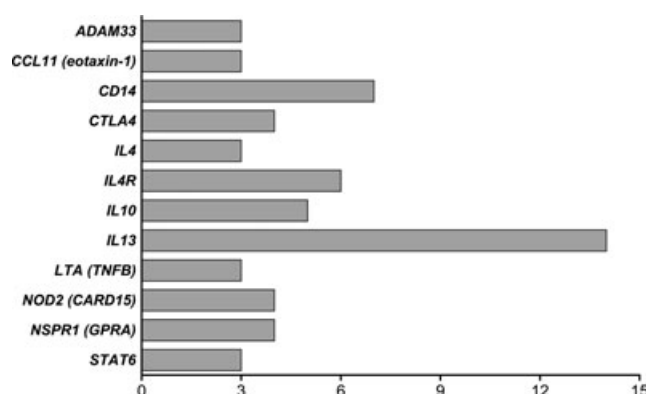


Fig. 4. Genes associated with total serum IgE levels in more than three independent non-GWA candidate gene studies. X-axis shows the numbers of the identified positive studies, whereas the names of the genes are depicted in y-axis. Only studies with more than five hundred genotyped participants were included. References underlying the figure can be found in Appendix S1.

### Markers of total serum IgE levels determined in genome-wide association studies

In the first genome-wide association study (GWAS), conducted by Weidinger et al. [160], loci on chromosomes 1q23, 5q31 and 12q13 were found to be consistently associated with total serum IgE levels in a discovery cohort and in subsequent replication in about 10 000 patients (Figs 1 and 3). Recently, the GABRIEL consortium GWAS [161] analysed total serum IgE levels in almost 15 000 patients, around half of whom were asthmatics. This large GWAS confirmed the association between chromosomes 1q23, 5q31 and 12q13 and total serum IgE levels, and two additional serum IgE susceptibility loci, 6p21.3 and 16p12, were identified (Figs 1 and 3) [161]. As GWAS is a hypothesis free approach, genes and genome regions not previously associated with a certain phenotype under investigation are frequently identified. In case of total serum IgE levels, GWAS hits represent known members of the IgE network and/or are (potentially) involved in IgE homeostasis (Figs 1 and 2). Herein, we discuss functional aspects of those loci and genes identified by GWAS.

#### Chromosome 1q23, *FCER1A*

The top serum IgE association hit from chromosome 1q23 [160] comprises *FCER1A*, the gene encoding the FcεRIα subunit of FcεRI. Associations with this locus were confirmed in subsequent studies [161–164], and *FCER1A* SNPs have already been investigated before GWAS [165] in American [166], Polish [167, 168] and Korean [169, 170] populations. All groups reported *FCER1A* polymorphisms to be associated with total and/or specific serum IgE levels. In addition, genetic

linkage had already been reported between 1q23 (or its close neighbourhood) and total serum IgE levels [171–173].

In GWAS, rs2251746 [160, 164] and rs2427837 [160] were found to be the two SNPs most significantly associated with total serum IgE levels. While the function of the SNP rs2427837 still remains unknown, the presence of the rs2251746 polymorphism minor allele results in the disruption of a GATA-1 binding site [174], which is in turn associated with the reduced activity of *FCER1A* proximal promoter [174, 175]. In Europeans, rs2251746 and rs2427837 are in tight linkage disequilibrium (LD;  $r^2 \geq 0.96$ ) [160, 162, 176]. Thus, it is difficult to dissect which SNP is causal.

In the GABRIEL Consortium GWAS on serum IgE, rs2252226 was the most significant SNP within the 1q23 locus. The variant is in LD with two SNPs previously shown to be functional, rs2427827 and rs2494262 ( $r^2$  in CEU of 0.97 and 0.77 respectively) [177–179]. Only recently, a SNP rs2494264 within this tagging bin (all  $r^2 > 0.73$  in CEU) [177–179] was reported to be strongly associated with total serum IgE levels [164]. SNP rs2427827 was shown to result in increased activity of the *FCER1A* proximal promoter [169, 175] due to replacement of weakly stimulating Sp1 (binding to the major allele) with the strong transcriptional activator HMG1/2 (binding to the minor allele) [175]. Alternatively, it was suggested that the higher activity of the *FCER1A* proximal promoter carrying the minor allele of rs2427827 SNP may result from preferential binding of inhibitory MAZ transcription factor to the major allele [169]. Nevertheless, the minor allele of rs2427827 was associated with increased FcεRI(α) expression on the basophil cell surface [175]. SNP rs2494262, located in the untranslated exon 1A of *FCER1A* [180], was reported to diminish transcriptional activity by increasing YY1 factor binding affinity [181].

Serum IgE levels positively correlate with FcεRI surface expression in different types of receptor-bearing cells [108, 182]. In addition, changes in free IgE levels in serum are reflected by altered FcεRI expression on cell surface, as demonstrated by clinical trials with omalizumab, an anti-IgE antibody [183, 184]. The mechanism of serum IgE-dependent FcεRI expression regulation is well known, although not yet fully understood [1, 185, 186]. IgE bound to FcεRI exerts a stabilizing effect on the receptor, most probably by preventing it from endocytosis and subsequent degradation or, less likely, by preventing its shedding [1, 185, 186]. However, genetic association between *FCER1A* SNPs and total serum IgE concentrations suggests alternative mechanisms for IgE regulation.

FcεRI may have a stabilizing effect on IgE turnover. Plasma half-life of IgE is very short [3], but a substantial portion of synthesized IgE is most probably bound

to FcεRI on basophils and mast cells. The half-life of FcεRI-bound IgE is approximately 14 days [3]. Thus, a genetic alteration of FcεRI expression levels on the surface of those cells may affect IgE stability and half-life. As a consequence, IgE serum levels may be influenced [187].

Alternatively, genetically determined higher FcεRI(α) expression on basophils and/or mast cells may enhance IgE-FcεRI(α)-mediated allergen-induced activation of those cells [187, 188]. In turn, increased secretion of IL-4 and IL-13 [189–192] and expression of CD40L [191, 193] by basophils and/or mast cells could stimulate further B cells to switch towards IgE production [1, 194].

It is also possible that a genotype-related increase in FcεRI expression on the surface of classical APCs may enhance their capacity to internalize allergens [188]. As a result, MHC class II-dependent presentation of the allergen to Th2 cells and their activation may increase and lead to subsequent enhancement of B-cell stimulation. In addition to classical APCs, basophils are also capable of presenting antigens to naïve T cells and Th2 cells as described in more details elsewhere [84–88, 194].

Considering that FcεRIα is an IgE-binding subunit of the receptor, genetic variants affecting its protein structure (missense or nonsense mutations) would be expected to be crucial for FcεRI function. So far, only very rare ( $\leq 3\%$ ) [160, 195] or even private [196] *FCER1A* missense mutations were reported in different ethnicities [160, 166, 196, 197]. These studies were restricted to coding exons and/or non-coding regulatory elements only [160, 166–169, 196, 197], but a systematic mutation screening of the full locus harbouring *FCER1A* is still missing.

#### *Chromosome 5q31, IL13, IL4, RAD50*

GWAS and family-based segregation studies show linkage between the chromosome 5q31 (5q, 5q31.1 or 5q31–33) and total serum IgE [160, 161, 164, 198–202]. Associations between *IL13* or *IL4* genetic polymorphisms and total serum IgE levels were observed in candidate gene studies [203–206], including those involving a systematic mutation screening of both genes [207, 208]. When concomitant effects of SNPs in IL-13/IL-4 pathway genes [including *IL13*, *IL4*, *IL4R* (encoding IL-4Rα) and *STAT6*] on total serum IgE levels were investigated, the risk to develop high levels of IgE was increasing with the number of functionally relevant SNPs in the pathway [209]. In addition, pairwise interactions between SNPs in *IL13* and *IL4R* [210] or *IL13* and *IL13RA1* [encoding IL-13Rα1 subunit of type II IL-4 (IL-4R)/IL-13 receptor (IL-13R)] [206] genes on total serum IgE levels were reported by the other investigators.

Functional properties of SNPs in *IL13* [211–216] and, to a lesser extent, in *IL4* have been reported [217]. *IL13* promoter SNPs rs1800925 [213, 216] and rs1881457 [214], which affect binding of transcription factors and promoter activity of *IL13*, are in high LD with three ( $r^2$  with rs1800925 in CEU: rs2706347, 0.81; rs7737470, 0.81; rs3798135, 0.81) and four ( $r^2$  with rs1881457 in CEU: rs2706347, 0.95; rs7737470, 0.95; rs3798135, 0.95; rs2040704, 0.90) top hits from the GWAS by Weidinger et al. respectively [160, 177–179]. The top IgE-associated polymorphism from 5q31 in the GABRIEL Consortium [161] and a further GWAS [164], rs20541, leads to a relevant amino acid change (R130Q), which has been investigated for its function in detail [60, 211, 212, 215, 216].

Considering the role of IL-13 and IL-4 in promoting CSR towards IgE, the GWAS association with total serum IgE levels seems not surprising [160, 161]. However, the 5q31 locus comprises not only *IL13* and *IL4*. Within a range of 150 kb, four genes are harboured in the locus: *IL5*, *RAD50*, *IL13* and *IL4*. *IL5* encodes for another Th2 cytokine. *RAD50*, a large gene spanning almost 90 kb, encodes for RAD50, an important DNA repair molecule. Interestingly, in the study by Weidinger et al. [160], SNPs showing the strongest association with total serum IgE from 5q31 were localized within *RAD50*, and not *IL13* or *IL4*. A later GWAS from the US also identified the *RAD50/IL13* region to be associated with asthma [218]. Subsequent analyses of several selected 5q31 SNPs demonstrated that those in *RAD50*, *IL13* or *IL4*, but not *IL5*, were associated with total serum IgE levels [218]. LD analyses in both studies [160, 218] showed that total serum IgE association signals in *RAD50* and *IL13* and/or *IL4* may be independent. Of note, *RAD50* function has not been related to asthma and IgE regulation previously, and it has not been studied in that context so far. This raises the question, how could a SNP located in a DNA repair gene play a role in IgE regulation?

One possible functional explanation for the position of the association signal in the *RAD50* gene locus may be that locus regulatory elements, which affect transcription of the nearby Th2 cytokine genes, *IL5*, *IL13* and *IL4*, are located within the realm of the *RAD50* gene [160, 218]. Gene expression within the complex 5q31 locus is co-ordinated and synchronized [219, 220]. Locus control regions (LCRs) are long regulatory regions that regulate the expression of linked genes in a copy number-dependent and tissue-specific manner [221]. They typically contain a cluster of tissue-specific DNase I hypersensitive sites (HS) involved in chromatin modelling [221]. In transgenic mice, in which *IL5*, *RAD50*, *IL13* and *IL4* are organized similar to the human chromosome 5q31, a Th2 LCR was detected [219, 220]. Four *RAD50* HS (RHS4–7) within 25 kb of

the 3' end of *RAD50* form the core region of the Th2 LCR [219, 222–225]. RHS5–7 are highly conserved between mice and human [222, 223, 226]. Indeed, two of the four SNPs showing the strongest association with total serum IgE in the study by Weidinger et al. [160] localize to human regions homologous to mouse RHS5 and RHS6 (rs3798135 and rs2040704 respectively), whereas the other two SNPs (rs2706347 and rs7737470) are in tight pairwise LD ( $r^2 \geq 0.85$ ) with polymorphisms located in human sequences corresponding to RHS5–7 [177–179, 219, 227].

It might also be speculated that the *RAD50* gene itself affects IgE regulation. *RAD50* is expressed ubiquitously. Together with MRE11 and NBS1, *RAD50* forms the MRE11-*RAD50*-NBS1 (MRN) complex, which is responsible for recognition and repair of double-strand DNA breaks [228–230]. Li et al. [218] suggested that the mechanism of allergy-related effects of *RAD50* SNPs might be related to the role of the MRN complex in somatic hypermutation (SHM). Indeed, the MRN complex is involved in SHM, a process that widens the spectrum of antigen recognition by antibodies [228, 231]. In addition, the MRN complex is involved in V(D)J recombination and class-switch recombination (CSR), two processes crucial for the development and function of B cells. In brief, during V(D)J recombination and CSR, the MRN complex recognizes DNA damage and may then direct cell to the cycle arrest where the required DNA repair can be subsequently conducted [229–231]. CSR is a critical step in the control of IgE synthesis which is under strict control. Hence, a contribution of the MRN complex to IgE regulation by influencing DNA breakage and repair in the process of CSR could explain the association between *RAD50* SNPs and total serum IgE levels. However, no functional data to support this hypothesis have been published yet.

#### *Chromosome 12q13, STAT6*

The serum IgE association signal from 12q13 most probably relates to the *STAT6* locus [160, 161, 164]. Already, studies conducted in the 1990s showed linkage between the chromosome 12q locus and total and/or specific IgE levels, although the peak of the signal was located rather in the 12q15–q24 region downstream of *STAT6* [232–235]. Subsequent candidate gene studies [236, 237], including a systematic mutation screening of the gene [238], showed associations between *STAT6* polymorphisms and total serum IgE concentrations. The intronic *STAT6* SNP rs324011 SNP was discovered to affect promoter activity by a silencing regulatory element (silencer) [239]. The rs324011 minor allele creates a binding site for the NF- $\kappa$ B transcription factor, increasing *STAT6* transcriptional activity. Moreover,

the minor allele of rs324011 was found to be associated with elevated expression of *STAT6* mRNA splicing variants in primary peripheral blood mononuclear cells [239]. SNP rs324011 is in tight LD with the most significant 12q13 hits as reported by Weidinger et al. [160] (rs12368672,  $r^2$  of 0.83), the GABRIEL Consortium [161] and the Framingham study [164] (rs167769,  $r^2$  of 0.96) [177–179].

#### Chromosome 6p21.3, *HLA-DRB1*

SNP rs9271300 showed the strongest association ( $P = 8.3 \times 10^{-15}$  vs.  $P \geq 8.5 \times 10^{-7}$ ) with serum IgE levels in the GABRIEL Consortium GWAS [161]. This SNP is located in the major histocompatibility complex (MHC) class II region between *HLA-DRB1* and *HLA-DQA1*. The GWAS result is in line with previous observations from genome-wide linkage searches that identified linkage between 6p/6p21/6p21.3 locus and total and/or specific serum IgE levels [234, 240, 241]. Candidate gene studies also reported associations between *HLA-DRB1/HLA-DRB1* alleles/markers and total and/or specific serum IgE levels [242–246].

MHC II molecules are expressed on the surface of professional and non-professional APCs where they present antigens to T cells [247, 248]. In their structure, MHC class II molecules are heterodimers composed of two non-covalently bound transmembrane subunits,  $\alpha$  and  $\beta$ , both encoded within the HLA locus [247, 248]. Details on the structure of MHC class II molecules [247, 248] and the complexity of the HLA locus [249] can be found elsewhere. *HLA-DR(B1)* variants may modulate antigen (allergen) presentation to T-helper cells, thus initiating Th2 differentiation and activation of CSR towards IgE in stimulated B cells. In addition, MHC class II and Fc $\epsilon$ R2 may interact in different forms of IgE/Fc $\epsilon$ R2-mediated allergen presentation [5, 132, 250]. B cells can be activated not only through binding of a specific antigen to their BCR but even by binding completely unrelated allergens through the IgE/Fc $\epsilon$ R2 complex if Fc $\epsilon$ R2 is expressed. Subsequent MHC class II-dependent presentation of more than one antigen may lead to inter-antigen epitope spreading [5, 129, 131, 251] relating to the clinical observation that in some atopic patients the number of allergens for which sensitization is present increases with the course and severity of the disease [131, 251]. Blocking IgE/Fc $\epsilon$ R2-mediated allergen presentation with non-IgE antibodies may thus prevent further development of the specific IgE repertoire and disease severity in atopic patients [252]. In a very recent GWAS in the Framingham cohort [164], several other genes from the HLA locus showed evidence of an association with total serum IgE levels, including *HLA-G*, *HLA-A* and *HLA-DQA2*.

#### Chromosome 16p12, *IL4R/IL21R*

SNP rs1859308 within the 16p12 locus was also associated with total serum IgE levels in GWAS [161]. The signal originates from a locus that harbours *IL4R* and *IL21R*. Both genes can potentially influence serum IgE (Fig. 1). IL-4 and IL-13 signal through receptors containing a IL-4R $\alpha$  subunit, for which *IL4R* codes. Not surprisingly, *IL4R* variants were a target of allergy genetics even before GWAS. *IL4R* SNPs were reported to be associated not only with total [253–258] and/or specific [255–257] serum IgE levels *per se* but also interacting with SNPs in other IL-4/IL-13/STAT6 pathway genes [209, 210]. Genetic variants in *IL4R* may affect ligand interaction and signal transmission [211, 255, 259].

Interleukin-21 (IL-21) belongs to a family of 'common  $\gamma$ -chain' ( $\gamma_c$ ) -dependent cytokines. Its functional receptor, IL-21R, is composed of a IL-21R( $\alpha$ ) subunit and  $\gamma_c$  [260–262]. IL-21 suppresses IgE production in mice [57, 263, 264]. *IL21R*-deficient mice had higher IgE synthesis [264], whereas in normal mice injected with IL-21, IgE production was reduced [263]. In humans, a stimulatory effect of IL-21 on IgE synthesis was reported [43, 265, 266]. Other studies identified IL-21 to either stimulate or inhibit human IgE synthesis, depending on circumstances [267, 268]. Taken together, effects of IL-21 on IgE production seem to be bidirectional [262, 267, 268]. SNP rs12934152 in *IL21R* promoter was shown to be associated with total serum IgE levels [269] and the magnitude of IL21 related inhibitory effects on IgE production by primary peripheral blood mononuclear cells [268].

#### Genetics of total serum IgE in respect to asthma and atopic dermatitis

IgE has been always thought to play a crucial role in the pathogenesis of 'allergic disorders', such as asthma and atopic dermatitis (AD). However, recent GWAS results show only a very little overlap between association signals for total serum IgE levels and asthma or atopic dermatitis [161, 270, 271]. In the large GABRIEL Consortium GWAS [161], the overlap between asthma and IgE signals was limited to 5q31 and 6p21.3. However, asthma (*HLA-DQB1*) and IgE (*HLA-DRB1*) signals from 6p21.3 seem to be rather independent of each other based on a weak LD between them, and the fact that the association between *HLA-DQB1* and asthma remained significant after adjustment for IgE levels [161].

Thus, genetic data may suggest that elevated serum IgE levels are a secondary epiphenomenon of asthma rather than its causal source [161]. Likewise, only a little overlap between GWAS for atopic dermatitis (AD)

and total serum IgE levels has been observed [271]. Also, genetic determinants of total serum IgE levels were not related to atopic diseases in recent candidate gene studies, e.g. on *FCER1A*, where no clear evidence for an association with asthma [160, 161], AD [160, 162, 163, 272, 273] or AR [160, 274] was found.

### Genetic regulation of specific serum IgE and/or atopic sensitization

So far, three GWA studies and one GWA meta-analysis attempted to identify genetic markers for atopy determined by specific serum IgE [275, 276]. Using a pooling-based GWAS approach in a small set of 75 atopics, equivalent asthmatics and controls, Castro-Giner et al. [275] found *SGK493* (*PKDCC*, 2p21), and potentially also *MAP3K5* (6q23.3), *COL29A1* (3q22.1) and *COL18A1* (21q22.3), to be associated with atopy (defined by specific serum IgE levels of  $> 0.35$  kU/L against *D. Pteronyssinus*, cat timothy grass or *C. herbarum*) and/or atopic asthma. Another study, conducted by Wan et al. [276], identified several loci associated with atopy (defined by specific serum IgE levels of  $\geq 0.35$  kU/L against house dust mite [Der p 1], mixed grass or cat fur): 8q12 (intergenic), 8q22 (*ANKRD46*), 10q26 (intergenic), 11q24 (*KIRREL3*), 13q14 (*FNDC3A*), 18q22 (*NETO1*) and 20p13 (intergenic). However, only the signal from the 11q24 locus (*KIRREL3*) could be replicated in at least one of three smaller replication cohorts in which atopic sensitization was analysed based on a positive skin prick test against typical inhalatory allergens [276]. In that study, SNPs associated with specific IgE also demonstrated an association with total serum IgE in the GWAS cohort (except for a variant in 11q24, *KIRREL3*), although with substantially smaller significance and lack of confirmation in replication cohorts [276]. The authors concluded that different genetic mechanisms underlie specific and total IgE production. None of the specific IgE signals reported by Castro-Giner et al. [275] or Wan et al. [276] correspond to those identified in GWAS-based studies on total serum IgE [160, 161]. Another recent GWAS from Singapore investigated atopy defined by positive skin prick test to house dust mite and other local allergens in a population of the Chinese ethnicity [277]. No individual SNP met the genome-wide significance level, but replication of the top 56 SNPs in a second population suggested rs8111930 in the *MRLP4* gene (19p13.2) and rs505010 upstream of the *BCAP* gene (10q24.1) to be associated with atopy [277].

Very recently, a first sufficiently powered genome-wide meta-analysis investigated GWAS data from four cohorts including in total more than 2000 sensitized

and 10 000 non-sensitized patients in relation to grass sensitization and allergic rhinitis. The definition of sensitization was standardized, although it differed between the cohorts as specific serum IgE in blood as well as skin prick test on mixed grasses or timothy grass and varying manufacturers and criteria for interpretation of specific IgE testing were combined [278]. The HLA region (6p21.32), *C11orf30/LRRC32* (11q13.5) and *TMEM232/SLCA25A46* (5q22.1) showed genome-wide significance for grass sensitization. Several further loci demonstrated suggestive, although non-significant associations [278]. Interestingly, the loci consistently shown to be associated with total serum IgE levels in GWA studies [160, 161, 164] from chromosomes 1q23, 5q31 and 12q13, were not among the most significant findings associated with grass sensitization [278].

Although general mechanisms of IgE regulation seem to be (more or less) known, it may still be difficult to characterize mechanisms leading to enhanced production of the certain specific IgE by a selected B-cell clone. Genetic studies on specific IgE/atopy [275–278] such as those focusing on specific sensitization [278], may help in understanding the mechanisms of specific IgE (dis-) regulation in general. At this point, it seems that an overlap between top GWAS signals for 'allergic' disorders, such as AD and especially AR, and specific IgE as well as atopy is stronger [277–279] than in the case of total serum IgE and asthma [161, 270, 271]. Further large and well-defined GWA studies on specific IgE with sufficient power are needed to assess the true role of genetic determinants on atopic sensitization. Only then further insight into the role of genetic IgE regulation and its impact on disease development may be gained.

### Acknowledgements

Daniel P. Potaczek wrote the first draft of the review and conducted systematic literature search. We are grateful to Sven Michel for preparation of Fig. 3 and to Vishwas Sharma for conducting 1000 Genomes-based LD analyses of SNPs in the human *RAD50* gene RHS5-7-homologous regions. This work was funded by the German Ministry of Education and Research (BMBF) as part of the National Genome Research Network (NGFN), with grant NGFN 01GS0810, and the German Research Council (DFG) by grant SFB587 project B16. The publication was screened for unintentional mistakes in quoting references using Plagiarism Detector software (<http://www.plagiarism-detector.com>).

**Conflict of interest:** The authors declare that they have no conflict of interest.

## References

- Macglashan D Jr IgE and Fc{epsilon}RI regulation. *Ann N Y Acad Sci* 2005; 1050:73–88.
- Kraft S, Kinet JP. New developments in FcepsilonRI regulation, function and inhibition. *Nat Rev Immunol* 2007; 7:365–78.
- Hellman L. Regulation of IgE homeostasis, and the identification of potential targets for therapeutic intervention. *Biomed Pharmacother* 2007; 61:34–49.
- Jackola DR, Liebel CL, Blumenthal MN, Rosenberg A. Random outcomes of allergen-specific responses in atopic families. *Clin Exp Allergy* 2004; 34:540–7.
- Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008; 8:205–17.
- Gould HJ, Sutton BJ, Beavil AJ, Beavil RL, McCloskey N, Coker HA *et al.* The biology of IgE and the basis of allergic disease. *Annu Rev Immunol* 2003; 21:579–628.
- Sicherer SH. Advances in anaphylaxis and hypersensitivity reactions to foods, drugs, and insect venom. *J Allergy Clin Immunol* 2003; 111:S829–34.
- Vernersson M, Aveskogh M, Hellman L. Cloning of IgE from the echidna (*Tachyglossus aculeatus*) and a comparative analysis of epsilon chains from all three extant mammalian lineages. *Dev Comp Immunol* 2004; 28:61–75.
- Vernersson M, Aveskogh M, Munday B, Hellman L. Evidence for an early appearance of modern post-switch immunoglobulin isotypes in mammalian evolution (II); cloning of IgE, IgG1 and IgG2 from a monotreme, the duck-billed platypus, *Ornithorhynchus anatinus*. *Eur J Immunol* 2002; 32:2145–55.
- Warr GW, Magor KE, Higgins DA. IgY: clues to the origins of modern antibodies. *Immunol Today* 1995; 16:392–8.
- Achatz G, Achatz-Straussberger G, Luger E, Lamers R, Cramer R. Regulation of the IgE response at the molecular level: impact on the development of systemic anti IgE therapeutic strategies. *Chem Immunol Allergy* 2006; 91:204–17.
- Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, Capron M *et al.* AllergoOncology: the role of IgE-mediated allergy in cancer. *Allergy* 2008; 63:1255–66.
- Conrad DH, Gibb DR, Sturgill J. Regulation of the IgE response. *F1000 Biol Rep* 2010; 2: pii:14.
- Gurish MF, Bryce PJ, Tao H, Kisselgof AB, Thornton EM, Miller HR *et al.* IgE enhances parasite clearance and regulates mast cell responses in mice infected with *Trichinella spiralis*. *J Immunol* 2004; 172:1139–45.
- King CL, Xianli J, Malhotra I, Liu S, Mahmoud AA, Oettgen HC. Mice with a targeted deletion of the IgE gene have increased worm burdens and reduced granulomatous inflammation following primary infection with *Schistosoma mansoni*. *J Immunol* 1997; 158:294–300.
- Fitzsimmons CM, McBeath R, Joseph S, Jones FM, Walter K, Hoffmann KF *et al.* Factors affecting human IgE and IgG responses to allergen-like *Schistosoma mansoni* antigens: molecular structure and patterns of *in vivo* exposure. *Int Arch Allergy Immunol* 2007; 142:40–50.
- Erb KJ. Helminths, allergic disorders and IgE-mediated immune responses: where do we stand? *Eur J Immunol* 2007; 37:1170–3.
- Trujillo-Vargas CM, Werner-Klein M, Wohlleben G, Polte T, Hansen G, Ehlers S *et al.* Helminth-derived products inhibit the development of allergic responses in mice. *Am J Respir Crit Care Med* 2007; 175:336–44.
- Feary J, Britton J, Leonardi-Bee J. Atopy and current intestinal parasite infection: a systematic review and meta-analysis. *Allergy* 2011; 66:569–78.
- Vouldoukis I, Mazier D, Moynet D, Thiolat D, Malvy D, Mossalayi MD. IgE mediates killing of intracellular toxoplasma gondii by human macrophages through CD23-Dependent, interleukin-10 sensitive pathway. *PLoS ONE* 2011; 6:e18289.
- Nigro EA, Brini AT, Soprana E, Ambrosi A, Dombrowicz D, Siccardi AG *et al.* Antitumor IgE adjuvanticity: key role of Fc epsilon RI. *J Immunol* 2009; 183:4530–6.
- Knittelfelder R, Riemer AB, Jensen-Jarolim E. Mimotope vaccination – from allergy to cancer. *Expert Opin Biol Ther* 2009; 9:493–506.
- Karagiannis P, Singer J, Hunt J, Gan SK, Rudman SM, Mechtcheriakova D *et al.* Characterisation of an engineered trastuzumab IgE antibody and effector cell mechanisms targeting HER2/neu-positive tumour cells. *Cancer Immunol Immunother* 2009; 58:915–30.
- Karagiannis SN, Bracher MG, Hunt J, McCloskey N, Beavil RL, Beavil AJ *et al.* IgE-antibody-dependent immunotherapy of solid tumors: cytotoxic and phagocytic mechanisms of eradication of ovarian cancer cells. *J Immunol* 2007; 179:2832–43.
- Rudman SM, Josephs DH, Cambrook H, Karagiannis P, Gilbert AE, Dodev T *et al.* Harnessing engineered antibodies of the IgE class to combat malignancy: initial assessment of Fc{epsilon}RI-mediated basophil activation by a tumour-specific IgE antibody to evaluate the risk of type I hypersensitivity. *Clin Exp Allergy* 2011; 41:1400–13.
- Lee JY, Park AK, Lee KM, Park SK, Han S, Han W *et al.* Candidate gene approach evaluates association between innate immunity genes and breast cancer risk in Korean women. *Carcinogenesis* 2009; 30:1528–31.
- Shen M, Vermeulen R, Rajaraman P, Menashe I, He X, Chapman RS *et al.* Polymorphisms in innate immunity genes and lung cancer risk in Xuanwei, China. *Environ Mol Mutagen* 2009; 50:285–90.
- Sutton BJ, Gould HJ. The human IgE network. *Nature* 1993; 366:421–8.
- Infuhr D, Cramer R, Lamers R, Achatz G. Molecular and cellular targets of anti-IgE antibodies. *Allergy* 2005; 60:977–85.
- Gonzalez D, van der Burg M, Garcia-Sanz R, Fenton JA, Langerak AW, Gonzalez M *et al.* Immunoglobulin gene rearrangements and the pathogenesis of multiple myeloma. *Blood* 2007; 110:3112–21.
- Arber DA. Molecular diagnostic approach to non-Hodgkin's lymphoma. *J Mol Diagn* 2000; 2:178–90.
- Bestagno M, Vangelista L, Mandiola PA, Mukherjee S, Sepulveda J, Burrone OR. Membrane immunoglobulins are stabilized by interchain disulfide bonds occurring within the extracel-

- lular membrane-proximal domain. *Biochemistry* 2001; **40**:10686–92.
- 33 Achatz G, Lamers M, Crameri R. Membrane bound IgE: the key receptor to restrict high IgE levels. *Open Immunol J* 2008; **1**:25–32.
  - 34 Batista FD, Efremov DG, Burrone OR. Characterization and expression of alternatively spliced IgE heavy chain transcripts produced by peripheral blood lymphocytes. *J Immunol* 1995; **154**:209–18.
  - 35 Batista FD, Efremov DG, Tkach T, Burrone OR. Characterization of the human immunoglobulin epsilon mRNAs and their polyadenylation sites. *Nucleic Acids Res* 1995; **23**:4805–11.
  - 36 Batista FD, Anand S, Presani G, Efremov DG, Burrone OR. The two membrane isoforms of human IgE assemble into functionally distinct B cell antigen receptors. *J Exp Med* 1996; **184**:2197–205.
  - 37 Dal Porto JM, Gauld SB, Merrell KT, Mills D, Pugh-Bernard AE, Cambier J. B cell antigen receptor signaling 101. *Mol Immunol* 2004; **41**:599–613.
  - 38 Poggianella M, Bestagno M, Burrone OR. The extracellular membrane-proximal domain of human membrane IgE controls apoptotic signaling of the B cell receptor in the mature B cell line A20. *J Immunol* 2006; **177**:3597–605.
  - 39 Schatz DG, Ji Y. Recombination centres and the orchestration of V(D)J recombination. *Nat Rev Immunol* 2011; **11**:251–63.
  - 40 Bacharier LB, Jabara H, Geha RS. Molecular mechanisms of immunoglobulin E regulation. *Int Arch Allergy Immunol* 1998; **115**:257–69.
  - 41 Kinoshita K, Honjo T. Linking class-switch recombination with somatic hypermutation. *Nat Rev Mol Cell Biol* 2001; **2**:493–503.
  - 42 Gould HJ, Beavil RL, Vercelli D. IgE isotype determination: epsilon-germline gene transcription, DNA recombination and B-cell differentiation. *Br Med Bull* 2000; **56**:908–24.
  - 43 Ozcan E, Notarangelo LD, Geha RS. Primary immune deficiencies with aberrant IgE production. *J Allergy Clin Immunol* 2008; **122**:1054–62.
  - 44 Stavnezer J. Molecular processes that regulate class switching. *Curr Top Microbiol Immunol* 2000; **245**:127–68.
  - 45 Kracker S, Durandy A. Insights into the B cell specific process of immunoglobulin class switch recombination. *Immunol Lett* 2011; **138**:97–103.
  - 46 Gould HJ, Takhar P, Harries HE, Durham SR, Corrigan CJ. Germinal-centre reactions in allergic inflammation. *Trends Immunol* 2006; **27**:446–52.
  - 47 Chaudhuri J, Alt FW. Class-switch recombination: interplay of transcription, DNA deamination and DNA repair. *Nat Rev Immunol* 2004; **4**:541–52.
  - 48 Martin A, Scharff MD. AID and mismatch repair in antibody diversification. *Nat Rev Immunol* 2002; **2**:605–14.
  - 49 Li Z, Woo CJ, Iglesias-Ussel MD, Ronai D, Scharff MD. The generation of antibody diversity through somatic hypermutation and class switch recombination. *Genes Dev* 2004; **18**:1–11.
  - 50 Stavnezer J, Guikema JE, Schrader CE. Mechanism and regulation of class switch recombination. *Annu Rev Immunol* 2008; **26**:261–92.
  - 51 Stavnezer J. Complex regulation and function of activation-induced cytidine deaminase. *Trends Immunol* 2011; **32**:194–201.
  - 52 Takhar P, Smurthwaite L, Coker HA, Fear DJ, Banfield GK, Carr VA *et al.* Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol* 2005; **174**:5024–32.
  - 53 Takhar P, Corrigan CJ, Smurthwaite L, O'Connor BJ, Durham SR, Lee TH *et al.* Class switch recombination to IgE in the bronchial mucosa of atopic and nonatopic patients with asthma. *J Allergy Clin Immunol* 2007; **119**:213–8.
  - 54 Fujieda S, Zhang K, Saxon A. IL-4 plus CD40 monoclonal antibody induces human B cells gamma subclass-specific isotype switch: switching to gamma 1, gamma 3, and gamma 4, but not gamma 2. *J Immunol* 1995; **155**:2318–28.
  - 55 Vercelli D. Immunoglobulin E and its regulators. *Curr Opin Allergy Clin Immunol* 2001; **1**:61–5.
  - 56 Yanagihara Y. Regulatory mechanisms of human IgE synthesis. *Allergology International* 2003; **52**:1–12.
  - 57 Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class-switch recombination. *Nat Rev Immunol* 2003; **3**:721–32.
  - 58 Monticelli S, Vercelli D. Molecular regulation of class switch recombination to IgE through epsilon germline transcription. *Allergy* 2001; **56**:270–8.
  - 59 Kuperman DA, Schleimer RP. Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma. *Curr Mol Med* 2008; **8**:384–92.
  - 60 Oh CK, Geba GP, Molfino N. Investigational therapeutics targeting the IL-4/IL-13/STAT-6 pathway for the treatment of asthma. *Eur Respir Rev* 2010; **19**:46–54.
  - 61 Goenka S, Kaplan MH. Transcriptional regulation by STAT6. *Immunol Res* 2011; **50**:87–96.
  - 62 Barnes PJ, Adcock IM. Transcription factors and asthma. *Eur Respir J* 1998; **12**:221–34.
  - 63 Hostager BS. Roles of TRAF6 in CD40 signaling. *Immunol Res* 2007; **39**:105–14.
  - 64 Oomizu S, Yanase Y, Suzuki H, Kameyoshi Y, Hide M. Fucoidan prevents C epsilon germline transcription and NFkappaB p52 translocation for IgE production in B cells. *Biochem Biophys Res Commun* 2006; **350**:501–7.
  - 65 Chen ZJ, Bhoj V, Seth RB. Ubiquitin, TAK1 and IKK: is there a connection?. *Cell Death Differ* 2006; **13**:687–92.
  - 66 Stutz AM, Woisetschlager M. Functional synergism of STAT6 with either NF-kappa B or PU.1 to mediate IL-4-induced activation of IgE germline gene transcription. *J Immunol* 1999; **163**:4383–91.
  - 67 Messner B, Stutz AM, Albrecht B, Peiritsch S, Woisetschlager M. Cooperation of binding sites for STAT6 and NF kappa B/rel in the IL-4-induced up-regulation of the human IgE germline promoter. *J Immunol* 1997; **159**:3330–7.
  - 68 Thienes CP, De Monte L, Monticelli S, Busslinger M, Gould HJ, Vercelli D. The transcription factor B cell-specific activator protein (BSAP) enhances both IL-4- and CD40-mediated activation of the human epsilon germline promoter. *J Immunol* 1997; **158**:5874–82.
  - 69 Monticelli S, Ghittoni R, Kabesch M, Vercelli D. Myb proteins repress human Ig epsilon germline transcription by inhibiting STAT6-dependent promoter activation. *Mol Immunol* 2002; **38**:1129–38.

- 70 Iciek LA, Delphin SA, Stavnezer J. CD40 cross-linking induces Ig epsilon germline transcripts in B cells via activation of NF-kappaB: synergy with IL-4 induction. *J Immunol* 1997; 158:4769–79.
- 71 Maizels N. Yin outwits Yang at the IgE locus. *Nat Immunol* 2003; 4:7–8.
- 72 Sugai M, Gonda H, Kusunoki T, Kataikai T, Yokota Y, Shimizu A. Essential role of Id2 in negative regulation of IgE class switching. *Nat Immunol* 2003; 4:25–30.
- 73 Gonda H, Sugai M, Nambu Y, Katakai T, Agata Y, Mori KJ *et al.* The balance between Pax5 and Id2 activities is the key to AID gene expression. *J Exp Med* 2003; 198:1427–37.
- 74 Dunnick WA, Shi J, Holden V, Fontaine C, Collins JT. The role of germline promoters and I exons in cytokine-induced gene-specific class switch recombination. *J Immunol* 2011; 186:350–8.
- 75 Vercelli D. Novel insights into class switch recombination. *Curr Opin Allergy Clin Immunol* 2002; 2:147–51.
- 76 Lee CG, Kinoshita K, Arudchandran A, Cerritelli SM, Crouch RJ, Honjo T. Quantitative regulation of class switch recombination by switch region transcription. *J Exp Med* 2001; 194:365–74.
- 77 Xu Z, Pone EJ, Al-Qahtani A, Park SR, Zan H, Casali P. Regulation of aicda expression and AID activity: relevance to somatic hypermutation and class switch DNA recombination. *Crit Rev Immunol* 2007; 27:367–97.
- 78 Longerich S, Basu U, Alt F, Storb U. AID in somatic hypermutation and class switch recombination. *Curr Opin Immunol* 2006; 18:164–74.
- 79 Horner AA, Jabara H, Ramesh N, Geha RS. gamma/delta T lymphocytes express CD40 ligand and induce isotype switching in B lymphocytes. *J Exp Med* 1995; 181:1239–44.
- 80 Jabara HH, Brodeur SR, Geha RS. Glucocorticoids upregulate CD40 ligand expression and induce CD40L-dependent immunoglobulin isotype switching. *J Clin Invest* 2001; 107:371–8.
- 81 Hajoui O, Janani R, Tulic M, Joubert P, Ronis T, Hamid Q *et al.* Synthesis of IL-13 by human B lymphocytes: regulation and role in IgE production. *J Allergy Clin Immunol* 2004; 114:657–63.
- 82 Sullivan BM, Locksley RM. Basophils: a nonredundant contributor to host immunity. *Immunity* 2009; 30:12–20.
- 83 Denzel A, Maus UA, Rodriguez Gomez M, Moll C, Niedermeier M, Winter C *et al.* Basophils enhance immunological memory responses. *Nat Immunol* 2008; 9:733–42.
- 84 Sokol CL, Medzhitov R. Role of basophils in the initiation of Th2 responses. *Curr Opin Immunol* 2010; 22:73–7.
- 85 Falcone FH, Knol EF, Gibbs BF. The role of basophils in the pathogenesis of allergic disease. *Clin Exp Allergy* 2011; 41:939–47.
- 86 Nakanishi K. Basophils are potent antigen-presenting cells that selectively induce Th2 cells. *Eur J Immunol* 2010; 40:1836–42.
- 87 Kawakami T. Basophils now enhance memory. *Nat Immunol* 2008; 9:720–1.
- 88 Sokol CL, Medzhitov R. Emerging functions of basophils in protective and allergic immune responses. *Mucosal Immunol* 2010; 3:129–37.
- 89 Sullivan BM, Liang HE, Bando JK, Wu D, Cheng LE, McKerrow JK *et al.* Genetic analysis of basophil function *in vivo*. *Nat Immunol* 2011; 12:527–35.
- 90 Locksley RM. Asthma and allergic inflammation. *Cell* 2010; 140:777–83.
- 91 KleinJan A, Vinke JG, Severijnen LW, Fokkens WJ. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J* 2000; 15:491–7.
- 92 Snow RE, Djukanovic R, Stevenson FK. Analysis of immunoglobulin E VH transcripts in a bronchial biopsy of an asthmatic patient confirms bias towards VH5, and indicates local clonal expansion, somatic mutation and isotype switch events. *Immunology* 1999; 98:646–51.
- 93 Vicario M, Blanchard C, Stringer KF, Collins MH, Mingler MK, Ahrens A *et al.* Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010; 59:12–20.
- 94 Smurthwaite L, Walker SN, Wilson DR, Birch DS, Merrett TG, Durham SR *et al.* Persistent IgE synthesis in the nasal mucosa of hay fever patients. *Eur J Immunol* 2001; 31:3422–31.
- 95 Gusareva ES, Ogorodova LM, Chernyak BA, Lipoldova M. Relationship between total and specific IgE in patients with asthma from Siberia. *J Allergy Clin Immunol* 2008; 121:781.
- 96 Erwin EA, Platts-Mills TA. Reply to “Relationship between total and specific IgE in patients with asthma from Siberia” (by Gusareva *et al.*, *J Allergy Clin Immunol* 2008;121:781). *J Allergy Clin Immunol* 2008; 121:781–2.
- 97 Erwin EA, Ronmark E, Wickens K, Perzanowski MS, Barry D, Lundback B *et al.* Contribution of dust mite and cat specific IgE to total IgE: relevance to asthma prevalence. *J Allergy Clin Immunol* 2007; 119:359–65.
- 98 Tsai LC, Tang RB, Hung MW, Chen HM, Hwang LA. Correlation between serum IgE and specific IgE antibody titer to house dust mite in children with asthma. *J Asthma* 1988; 25:7–13.
- 99 Bruhns P, Fremont S, Daeron M. Regulation of allergy by Fc receptors. *Curr Opin Immunol* 2005; 17:662–9.
- 100 Zhang M, Murphy RF, Agrawal DK. Decoding IgE Fc receptors. *Immunol Res* 2007; 37:1–16.
- 101 Bieber T. The pro- and anti-inflammatory properties of human antigen-presenting cells expressing the high affinity receptor for IgE (Fc epsilon RI). *Immunobiology* 2007; 212:499–503.
- 102 Borland G, Edkins AL, Acharya M, Matheson J, White LJ, Allen JM *et al.* Alphavbeta5 integrin sustains growth of human pre-B cells through an RGD-independent interaction with a basic domain of the CD23 protein. *J Biol Chem* 2007; 282:27315–26.
- 103 Chen HY, Sharma BB, Yu L, Zuberi R, Weng IC, Kawakami Y *et al.* Role of galectin-3 in mast cell functions: galectin-3-deficient mast cells exhibit impaired mediator release and defective JNK expression. *J Immunol* 2006; 177:4991–7.
- 104 Platzer B, Ruiter F, van der Mee J, Fiebigier E. Soluble IgE receptors-elements of the IgE network. *Immunol Lett* 2011; 141:36–44.
- 105 Kinet JP. The high-affinity IgE receptor (Fc epsilon RI): from physiology to pathology. *Annu Rev Immunol* 1999; 17:931–72.
- 106 Blank U, Ra C, Miller L, White K, Metzger H, Kinet JP. Complete structure and expression in transfect-

- ed cells of high affinity IgE receptor. *Nature* 1989; 337:187–9.
- 107 Maurer D, Fiebiger E, Reininger B, Wolff-Winiski B, Jouvin MH, Kilgus O *et al.* Expression of functional high affinity immunoglobulin E receptors (Fc epsilon RI) on monocytes of atopic individuals. *J Exp Med* 1994; 179:745–50.
  - 108 Foster B, Metcalfe DD, Prussin C. Human dendritic cell 1 and dendritic cell 2 subsets express FcepsilonRI: correlation with serum IgE and allergic asthma. *J Allergy Clin Immunol* 2003; 112:1132–8.
  - 109 Novak N, Allam JP, Hagemann T, Jenneck C, Laffer S, Valenta R *et al.* Characterization of FcepsilonRI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. *J Allergy Clin Immunol* 2004; 114:364–70.
  - 110 Hulett MD, Brinkworth RI, McKenzie IF, Hogarth PM. Fine structure analysis of interaction of FcepsilonRI with IgE. *J Biol Chem* 1999; 274:13345–52.
  - 111 Garman SC, Sechi S, Kinet JP, Jar-detzky TS. The analysis of the human high affinity IgE receptor Fc epsilon RI alpha from multiple crystal forms. *J Mol Biol* 2001; 311:1049–62.
  - 112 Wilson BS, Kapp N, Lee RJ, Pfeiffer JR, Martinez AM, Platt Y *et al.* Distinct functions of the Fc epsilon R1 gamma and beta subunits in the control of Fc epsilon R1-mediated tyrosine kinase activation and signaling responses in RBL-2H3 mast cells. *J Biol Chem* 1995; 270:4013–22.
  - 113 Kraft S, Rana S, Jouvin MH, Kinet JP. The role of the FcepsilonRI beta-chain in allergic diseases. *Int Arch Allergy Immunol* 2004; 135:62–72.
  - 114 Winter WE, Hardt NS, Fuhrman S. Immunoglobulin E: importance in parasitic infections and hypersensitivity responses. *Arch Pathol Lab Med* 2000; 124:1382–5.
  - 115 Maurer D, Fiebiger S, Ebner C, Reininger B, Fischer GF, Wichlas S *et al.* Peripheral blood dendritic cells express Fc epsilon RI as a complex composed of Fc epsilon RI alpha- and Fc epsilon RI gamma-chains and can use this receptor for IgE-mediated allergen presentation. *J Immunol* 1996; 157:607–16.
  - 116 Bieber T, Kraft S, Jurgens M, Strobel I, Haberstock J, Tomov H *et al.* New insights in the structure and biology of the high affinity receptor for IgE (Fc epsilon RI) on human epidermal langerhans cells. *J Dermatol Sci* 1996; 13:71–5.
  - 117 Dehlink E, Platzer B, Baker AH, Larosa J, Pardo M, Dwyer P *et al.* A soluble form of the high affinity IgE receptor, Fc-epsilon-RI, circulates in human serum. *PLoS ONE* 2011; 6: e19098.
  - 118 Acharya M, Borland G, Edkins AL, Maclellan LM, Matheson J, Ozanne BW *et al.* CD23/FcepsilonRII: molecular multi-tasking. *Clin Exp Immunol* 2010; 162:12–23.
  - 119 Beavil AJ, Edmeades RL, Gould HJ, Sutton BJ. Alpha-helical coiled-coil stalks in the low-affinity receptor for IgE (Fc epsilon RII/CD23) and related C-type lectins. *Proc Natl Acad Sci U S A* 1992; 89:753–7.
  - 120 Ewart MA, Ozanne BW, Cushley W. The CD23a and CD23b proximal promoters display different sensitivities to exogenous stimuli in B lymphocytes. *Genes Immun* 2002; 3:158–64.
  - 121 Yokota A, Yukawa K, Yamamoto A, Sugiyama K, Suemura M, Tashiro Y *et al.* Two forms of the low-affinity Fc receptor for IgE differentially mediate endocytosis and phagocytosis: identification of the critical cytoplasmic domains. *Proc Natl Acad Sci U S A* 1992; 89:5030–4.
  - 122 Suter U, Texido G, Hofstetter H. Expression of human lymphocyte IgE receptor (Fc epsilon RII/CD23). Identification of the Fc epsilon RIIa promoter and its functional analysis in B lymphocytes. *J Immunol* 1989; 143:3087–92.
  - 123 Conrad DH, Ford JW, Sturgill JL, Gibb DR. CD23: an overlooked regulator of allergic disease. *Curr Allergy Asthma Rep* 2007; 7:331–7.
  - 124 Gould HJ, Takhar P, Harries HE, Chevretton E, Sutton BJ. The allergic march from *Staphylococcus aureus* superantigens to immunoglobulin E. *Chem Immunol Allergy* 2007; 93:106–36.
  - 125 Hibbert RG, Teriete P, Grundy GJ, Beavil RL, Reljic R, Holers VM *et al.* The structure of human CD23 and its interactions with IgE and CD21. *J Exp Med* 2005; 202:751–60.
  - 126 McCloskey N, Hunt J, Beavil RL, Jut-ton MR, Grundy GJ, Girardi E *et al.* Soluble CD23 monomers inhibit and oligomers stimulate IGE synthesis in human B cells. *J Biol Chem* 2007; 282:24083–91.
  - 127 Bowles SL, Jaeger C, Ferrara C, Fingerth J, Van De Venter M, Oosthuizen V. Comparative binding of soluble fragments (derCD23, sCD23, and exCD23) of recombinant human CD23 to CD21 (SCR 1-2) and native IgE, and their effect on IgE regulation. *Cell Immunol* 2011; 271:371–8.
  - 128 Cheng LE, Wang ZE, Locksley RM. Murine B cells regulate serum IgE levels in a CD23-dependent manner. *J Immunol* 2010; 185:5040–7.
  - 129 Mudde GC, Bheekha R, Bruijnzeel-Ko-omen CA. IgE-mediated antigen pre-sentation. *Allergy* 1995; 50:193–9.
  - 130 Santamaria LF, Bheekha R, van Reij-sen FC, Perez Soler MT, Suter M, Bru-ijnzeel-Koomen CA *et al.* Antigen focusing by specific monomeric immunoglobulin E bound to CD23 on Epstein-Barr virus-transformed B cells. *Hum Immunol* 1993; 37:23–30.
  - 131 Mudde GC, Bheekha R, Bruijnzeel-Ko-omen CA. Consequences of IgE/CD23-mediated antigen presentation in allergy. *Immunol Today* 1995; 16: 380–3.
  - 132 Karagiannis SN, Warrack JK, Jen-nings KH, Murdock PR, Christie G, Moulder K *et al.* Endocytosis and recycling of the complex between CD23 and HLA-DR in human B cells. *Immunology* 2001; 103:319–31.
  - 133 Palmer LJ, Pare PD, Faux JA, Moffatt MF, Daniels SE, LeSouef PN *et al.* Fc epsilon R1-beta polymorphism and total serum IgE levels in endemically parasitized Australian aborigines. *Am J Hum Genet* 1997; 61:182–8.
  - 134 Orszczyn MP, Annesi-Maesano I, Charpin D, Paty E, Maccario J, Kauff-mann F. Relationships of active and passive smoking to total IgE in adults of the epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness, and atopy (EGEA). *Am J Respir Crit Care Med* 2000; 161:1241–6.
  - 135 Mediaty A, Neuber K. Total and spe-cific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis. *Immun Ageing* 2005; 2:9.
  - 136 Grundbacher FJ. Causes of variation in serum IgE levels in normal popula-

- tions. *J Allergy Clin Immunol* 1975; **56**:104–11.
- 137 Grundbacher FJ, Massie FS. Levels of immunoglobulin G, M, A, and E at various ages in allergic and nonallergic black and white individuals. *J Allergy Clin Immunol* 1985; **75**: 651–8.
  - 138 Hanson B, McGue M, Roitman-Johnson B, Segal NL, Bouchard TJ Jr, Blumenthal MN. Atopic disease and immunoglobulin E in twins reared apart and together. *Am J Hum Genet* 1991; **48**:873–9.
  - 139 Palmer LJ, Burton PR, Faux JA, James AL, Musk AW, Cookson WO. Independent inheritance of serum immunoglobulin E concentrations and airway responsiveness. *Am J Respir Crit Care Med* 2000; **161**:1836–43.
  - 140 Jacobsen HP, Herskind AM, Nielsen BW, Husby S. IgE in unselected like-sexed monozygotic and dizygotic twins at birth and at 6 to 9 years of age: high but dissimilar genetic influence on IgE levels. *J Allergy Clin Immunol* 2001; **107**:659–63.
  - 141 Strachan DP, Wong HJ, Spector TD. Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. *J Allergy Clin Immunol* 2001; **108**:901–7.
  - 142 Hasstedt SJ, Meyers DA, Marsh DG. Inheritance of immunoglobulin E: genetic model fitting. *Am J Med Genet* 1983; **14**:61–6.
  - 143 Marsh DG, Bias WB, Ishizaka K. Genetic control of basal serum immunoglobulin E level and its effect on specific reagenic sensitivity. *Proc Natl Acad Sci U S A* 1974; **71**:3588–92.
  - 144 Meyers DA, Freidhoff LR, Marsh DG. Predicting skin test sensitivity and total serum IgE levels in family members. *J Allergy Clin Immunol* 1986; **77**:608–15.
  - 145 Altin J, Shen C, Liston A. Understanding the genetic regulation of IgE production. *Blood Rev* 2010; **24**:163–9.
  - 146 Liston A, Enders A, Siggs OM. Unravelling the association of partial T-cell immunodeficiency and immune dysregulation. *Nat Rev Immunol* 2008; **8**:545–58.
  - 147 Minegishi Y. Hyper-IgE syndrome. *Curr Opin Immunol* 2009; **21**:487–92.
  - 148 Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL et al. Hyper-IgE syndrome with recurrent infections – an autosomal dominant multisystem disorder. *N Engl J Med* 1999; **340**:692–702.
  - 149 Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr* 2004; **144**: 93–9.
  - 150 Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature* 2007; **448**:1058–62.
  - 151 Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* 2007; **357**:1608–19.
  - 152 Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* 2006; **25**:745–55.
  - 153 Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ et al. Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med* 2009; **361**:2046–55.
  - 154 Wjst M, Lichtner P, Meitinger T, Grimbacher B. STAT3 single-nucleotide polymorphisms and STAT3 mutations associated with hyper-IgE syndrome are not responsible for increased serum IgE serum levels in asthma families. *Eur J Hum Genet* 2009; **17**:352–6.
  - 155 Altin JA, Tian L, Liston A, Bertram EM, Goodnow CC, Cook MC. Decreased T-cell receptor signaling through CARD11 differentially compromises forkhead box protein 3-positive regulatory versus T(H)2 effector cells to cause allergy. *J Allergy Clin Immunol* 2011; **127**:1277–85.
  - 156 Zhang L, Zhang Y, Desrosiers M, Wang C, Zhao Y, Han D. Genetic association study of FOXP3 polymorphisms in allergic rhinitis in a Chinese population. *Hum Immunol* 2009; **70**:930–4.
  - 157 Suttner K, Depner M, Wetzke M, Klopp N, von Mutius E, Illig T et al. Genetic variants harbored in the forkhead box protein 3 locus increase hay fever risk. *J Allergy Clin Immunol* 2010; **125**:1395–9.
  - 158 Fodor E, Garacz E, Polyanka H, Koreck A, Kemeny L, Szell M. The rs3761548 polymorphism of FOXP3 is a protective genetic factor against allergic rhinitis in the Hungarian female population. *Hum Immunol* 2011; **72**:926–9.
  - 159 <http://www.ncbi.nlm.nih.gov/pubmed>.
  - 160 Weidinger S, Gieger C, Rodriguez E, Baurecht H, Mempel M, Klopp N et al. Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus. *PLoS Genet* 2008; **4**:e1000166.
  - 161 Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010; **363**:1211–21.
  - 162 Chen CM, Weidinger S, Klopp N, Sauenthaler S, Bischof W, Herbarth O et al. Common variants in FCER1A influence total serum IgE levels from cord blood up to six years of life. *Allergy* 2009; **64**:1327–32.
  - 163 Mahachie John JM, Baurecht H, Rodriguez E, Naumann A, Wagenpfeil S, Klopp N et al. Analysis of the high affinity IgE receptor genes reveals epistatic effects of FCER1A variants on eczema risk. *Allergy* 2010; **65**:875–82.
  - 164 Granada M, Wilk JB, Tuzova M, Strachan DP, Weidinger S, Albrecht E et al. A genome-wide association study of plasma total IgE concentrations in the Framingham heart study. *J Allergy Clin Immunol* 2011; DOI: 10.1016/j.jaci.2011.09.029.
  - 165 Akhbari L, Sandford AJ. Genome-wide association studies for discovery of genes involved in asthma. *Respirology* 2011; **16**:396–406.
  - 166 Shikanai T, Silverman ES, Morse BW, Lilly CM, Inoue H, Drazen JM. Sequence variants in the FcepsilonRI alpha chain gene. *J Appl Physiol* 2002; **93**:37–41.
  - 167 Potaczek DP, Sanak M, Mastalerz L, Setkowicz M, Kaczor M, Nizankowska E et al. The alpha-chain of high-affinity receptor for IgE (FcepsilonRI-alpha) gene polymorphisms and serum IgE levels. *Allergy* 2006; **61**:1230–3.
  - 168 Potaczek DP, Sanak M, Mastalerz L, Milewski M, Gawlewicz-Mroccka A,

- Szczeklik A. Genetic polymorphisms of the novel FCER1A gene region: relation to total serum IgE levels. *Ann Allergy Asthma Immunol* 2007; 98:500–1.
- 169 Bae JS, Kim SH, Ye YM, Yoon HJ, Suh CH, Nahm DH *et al.* Significant association of FcepsilonRIalpha promoter polymorphisms with aspirin-intolerant chronic urticaria. *J Allergy Clin Immunol* 2007; 119:449–56.
- 170 Palikhe N, Kim SH, Yang EM, Kang YM, Ye YM, Hur GY *et al.* Analysis of high-affinity IgE receptor (FcepsilonRI) polymorphisms in patients with aspirin-intolerant chronic urticaria. *Allergy Asthma Proc* 2008; 29:250–7.
- 171 Xu X, Fang Z, Wang B, Chen C, Guang W, Jin Y *et al.* A genomewide search for quantitative-trait loci underlying asthma. *Am J Hum Genet* 2001; 69:1271–7.
- 172 Altmüller J, Seidel C, Lee YA, Loesgen S, Bulle D, Friedrichs F *et al.* Phenotypic and genetic heterogeneity in a genome-wide linkage study of asthma families. *BMC Pulm Med* 2005; 5:1.
- 173 Webb BT, van den Oord E, Akkari A, Wilton S, Ly T, Duff R *et al.* Quantitative linkage genome scan for atopy in a large collection of Caucasian families. *Hum Genet* 2007; 121: 83–92.
- 174 Hasegawa M, Nishiyama C, Nishiyama M, Akizawa Y, Mitsuishi K, Ito T *et al.* A novel -66T/C polymorphism in Fc epsilon RI alpha-chain promoter affecting the transcription activity: possible relationship to allergic diseases. *J Immunol* 2003; 171:1927–33.
- 175 Kanada S, Nakano N, Potaczek DP, Maeda K, Shimokawa N, Niwa Y *et al.* Two different transcription factors discriminate the -315C>T polymorphism of the Fc epsilon RI alpha gene: binding of Sp1 to -315C and of a high mobility group-related molecule to -315T. *J Immunol* 2008; 180:8204–10.
- 176 Potaczek DP, Kamijo M, Hara M, Okumura K, Undas A, Nishiyama C. A comparative search for human FcepsilonRIalpha gene (FCER1A) 3'-UTR polymorphisms in Japanese and Polish populations. *Mol Biol Rep* 2011; DOI: 10.1007/s11033-011-1150-2.
- 177 Johnson AD, Handsaker RE, Pulit SL, Nizzari MM, O'Donnell CJ, de Bakker PI. SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics* 2008; 24:2938–9.
- 178 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* 2010; 467:1061–73.
- 179 <http://www.broadinstitute.org/mpg/snap/ldsearch.php>.
- 180 Hasegawa M, Nishiyama C, Nishiyama M, Akizawa Y, Takahashi K, Ito T *et al.* Regulation of the human Fc epsilon RI alpha-chain distal promoter. *J Immunol* 2003; 170:3732–8.
- 181 Potaczek DP, Maeda K, Wang QH, Nakano N, Kanada S, Stepień E *et al.* FcepsilonRIalpha gene -18483A>C polymorphism affects transcriptional activity through YY1 binding. *Immunogenetics* 2009; 61:649–55.
- 182 Sihra BS, Kon OM, Grant JA, Kay AB. Expression of high-affinity IgE receptors (Fc epsilon RI) on peripheral blood basophils, monocytes, and eosinophils in atopic and nonatopic subjects: relationship to total serum IgE concentrations. *J Allergy Clin Immunol* 1997; 99:699–706.
- 183 Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcepsilonRI expression. *J Allergy Clin Immunol* 2003; 112:1147–54.
- 184 Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA *et al.* Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils. *J Allergy Clin Immunol* 2004; 113:297–302.
- 185 Hamilton RG, MacGlashan DW Jr, Saini SS. IgE antibody-specific activity in human allergic disease. *Immunol Res* 2010; 47:273–84.
- 186 MacGlashan DW Jr. Endocytosis, recycling, and degradation of unoccupied FcepsilonRI in human basophils. *J Leukoc Biol* 2007; 82:1003–10.
- 187 Sanak M, Potaczek DP, Nizankowska-Mogilnicka E, Szczeklik A. Genetic variability of the high-affinity IgE receptor alpha subunit (Fc epsilon RI alpha) is related to total serum IgE levels in allergic subjects. *Allergol Int* 2007; 56:397–401.
- 188 Potaczek DP, Nishiyama C, Sanak M, Szczeklik A, Okumura K. Genetic variability of the high-affinity IgE receptor alpha-subunit (FcepsilonRIalpha). *Immunol Res* 2009; 45:75–84.
- 189 MacGlashan D Jr, White JM, Huang SK, Ono SJ, Schroeder JT, Lichtenstein LM. Secretion of IL-4 from human basophils. The relationship between IL-4 mRNA and protein in resting and stimulated basophils. *J Immunol* 1994; 152:3006–16.
- 190 Burd PR, Thompson WC, Max EE, Mills FC. Activated mast cells produce interleukin 13. *J Exp Med* 1995; 181:1373–80.
- 191 Henz BM, Maurer M, Lippert U, Worm M, Babina M. Mast cells as initiators of immunity and host defense. *Exp Dermatol* 2001; 10:1–10.
- 192 Horsmanheimo L, Harvima IT, Jarvikallio A, Harvima RJ, Naukkarinen A, Horsmanheimo M. Mast cells are one major source of interleukin-4 in atopic dermatitis. *Br J Dermatol* 1994; 131:348–53.
- 193 Yanagihara Y, Kajiwaru K, Basaki Y, Ikizawa K, Ebisawa M, Ra C *et al.* Cultured basophils but not cultured mast cells induce human IgE synthesis in B cells after immunologic stimulation. *Clin Exp Immunol* 1998; 111:136–43.
- 194 Schneider E, Thieblemont N, De Moraes ML, Dy M. Basophils: new players in the cytokine network. *Eur Cytokine Netw* 2010; 21:142–53.
- 195 Potaczek DP, Nastalek M, Wojas-Pelc A, Okumura K, Undas A, Nishiyama C. Naturally occurring FCER1A N222K mutation - its ethnicity-dependent distribution and a role in atopic dermatitis. *Mol Immunol* 2011; 48:979–80.
- 196 Potaczek DP, Sanak M, Mastalerz L, Szczeklik A. Coding region for the high affinity receptor of immunoglobulin E is highly conservative in allergic patients. *Clin Exp Allergy* 2007; 37:1574–5.
- 197 Kim YK, Park HW, Yang JS, Oh SY, Chang YS, Shin ES *et al.* Association and functional relevance of E237G, a polymorphism of the high-affinity immunoglobulin E-receptor beta chain gene, to airway hyper-responsiveness. *Clin Exp Allergy* 2007; 37:592–8.
- 198 Marsh DG, Neely JD, Breazeale DR, Ghosh B, Freidhoff LR, Ehrlich-Kautzky E *et al.* Linkage analysis of IL4 and other chromosome 5q31.1

- markers and total serum immunoglobulin E concentrations. *Science* 1994; 264:1152–6.
- 199 Marsh DG, Neely JD, Breazeale DR, Ghosh B, Friedhoff LR, Schou C *et al.* Total serum IgE levels and chromosome 5q. *Clin Exp Allergy* 1995; 25 (Suppl. 2):79–83.
  - 200 Meyers DA, Postma DS, Panhuysen CI, Xu J, Amelung PJ, Levitt RC *et al.* Evidence for a locus regulating total serum IgE levels mapping to chromosome 5. *Genomics* 1994; 23:464–70.
  - 201 Xu J, Levitt RC, Panhuysen CI, Postma DS, Taylor EW, Amelung PJ *et al.* Evidence for two unlinked loci regulating total serum IgE levels. *Am J Hum Genet* 1995; 57:425–30.
  - 202 Xu J, Postma DS, Howard TD, Koppelman GH, Zheng SL, Stine OC *et al.* Major genes regulating total serum immunoglobulin E levels in families with asthma. *Am J Hum Genet* 2000; 67:1163–73.
  - 203 Maier LM, Howson JM, Walker N, Spickett GP, Jones RW, Ring SM *et al.* Association of IL13 with total IgE: evidence against an inverse association of atopy and diabetes. *J Allergy Clin Immunol* 2006; 117:1306–13.
  - 204 Chan IH, Leung TF, Tang NL, Li CY, Sung YM, Wong GW *et al.* Gene-gene interactions for asthma and plasma total IgE concentration in Chinese children. *J Allergy Clin Immunol* 2006; 117:127–33.
  - 205 Liu X, Beaty TH, Deindl P, Huang SK, Lau S, Sommerfeld C *et al.* Associations between total serum IgE levels and the 6 potentially functional variants within the genes IL4, IL13, and IL4RA in German children: the German multicenter atopy study. *J Allergy Clin Immunol* 2003; 112:382–8.
  - 206 Kim HB, Lee YC, Lee SY, Jung J, Jin HS, Kim JH *et al.* Gene-gene interaction between IL-13 and IL-13Ralpha1 is associated with total IgE in Korean children with atopic asthma. *J Hum Genet* 2006; 51:1055–62.
  - 207 Graves PE, Kabesch M, Halonen M, Holberg CJ, Baldini M, Fritzsche C *et al.* A cluster of seven tightly linked polymorphisms in the IL-13 gene is associated with total serum IgE levels in three populations of white children. *J Allergy Clin Immunol* 2000; 105:506–13.
  - 208 Kabesch M, Tzotcheva I, Carr D, Hoffer C, Weiland SK, Fritzsche C *et al.* A complete screening of the IL4 gene: novel polymorphisms and their association with asthma and IgE in childhood. *J Allergy Clin Immunol* 2003; 112:893–8.
  - 209 Kabesch M, Schedel M, Carr D, Woitsch B, Fritzsche C, Weiland SK *et al.* IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol* 2006; 117:269–74.
  - 210 Howard TD, Koppelman GH, Xu J, Zheng SL, Postma DS, Meyers DA *et al.* Gene-gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. *Am J Hum Genet* 2002; 70:230–6.
  - 211 Chen W, Ericksen MB, Levin LS, Khurana Hershey GK. Functional effect of the R110Q IL13 genetic variant alone and in combination with IL4RA genetic variants. *J Allergy Clin Immunol* 2004; 114:553–60.
  - 212 Vladich FD, Brazille SM, Stern D, Peck ML, Ghittoni R, Vercelli D. IL-13 R130Q, a common variant associated with allergy and asthma, enhances effector mechanisms essential for human allergic inflammation. *J Clin Invest* 2005; 115:747–54.
  - 213 Cameron L, Webster RB, Strempel JM, Kiesler P, Kabesch M, Ramachandran H *et al.* Th2 cell-selective enhancement of human IL13 transcription by IL13-1112C>T, a polymorphism associated with allergic inflammation. *J Immunol* 2006; 177:8633–42.
  - 214 Kiesler P, Shakya A, Tantin D, Vercelli D. An allergy-associated polymorphism in a novel regulatory element enhances IL13 expression. *Hum Mol Genet* 2009; 18:4513–20.
  - 215 Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008; 8:169–82.
  - 216 Vercelli D. Genetic regulation of IgE responses: Achilles and the tortoise. *J Allergy Clin Immunol* 2005; 116:60–4.
  - 217 Rosenwasser LJ, Klemm DJ, Dresback JK, Inamura H, Mascali JJ, Klennert M *et al.* Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. *Clin Exp Allergy* 1995; 25 (Suppl. 2):74–8.
  - 218 Li X, Howard TD, Zheng SL, Haselkorn T, Peters SP, Meyers DA *et al.* Genome-wide association study of asthma identifies RAD50-IL13 and HLA-DR/DQ regions. *J Allergy Clin Immunol* 2010; 125:328–35.
  - 219 Fields PE, Lee GR, Kim ST, Bartsevich VV, Flavell RA. Th2-specific chromatin remodeling and enhancer activity in the Th2 cytokine locus control region. *Immunity* 2004; 21:865–76.
  - 220 Lee GR, Fields PE, Griffin TJ, Flavell RA. Regulation of the Th2 cytokine locus by a locus control region. *Immunity* 2003; 19:145–53.
  - 221 Li Q, Peterson KR, Fang X, Stamatiyannopoulos G, Locus control regions. *Blood* 2002; 100:3077–86.
  - 222 Wilson CB, Rowell E, Sekimata M. Epigenetic control of T-helper-cell differentiation. *Nat Rev Immunol* 2009; 9:91–105.
  - 223 Lee GR, Kim ST, Spilianakis CG, Fields PE, Flavell RA. T helper cell differentiation: regulation by cis elements and epigenetics. *Immunity* 2006; 24:369–79.
  - 224 Amsen D, Spilianakis CG, Flavell RA. How are T(H)1 and T(H)2 effector cells made? *Curr Opin Immunol* 2009; 21:153–60.
  - 225 Lee GR, Spilianakis CG, Flavell RA. Hypersensitive site 7 of the TH2 locus control region is essential for expressing TH2 cytokine genes and for long-range intrachromosomal interactions. *Nat Immunol* 2005; 6:42–8.
  - 226 Strempel JM, Grenningloh R, Ho IC, Vercelli D. Phylogenetic and functional analysis identifies Ets-1 as a novel regulator of the Th2 cytokine gene locus. *J Immunol* 2010; 184:1309–16.
  - 227 <http://www.1000genomes.org/>.
  - 228 Yabuki M, Fujii MM, Maizels N. The MRE11-RAD50-NBS1 complex accelerates somatic hypermutation and gene conversion of immunoglobulin variable regions. *Nat Immunol* 2005; 6:730–6.
  - 229 Kinoshita E, van der Linden E, Sanchez H, Wyman C. RAD50, an SMC family member with multiple roles in DNA break repair: how does ATP affect function? *Chromosome Res* 2009; 17:277–88.
  - 230 Xu Y. DNA damage: a trigger of innate immunity but a requirement for adaptive immune homeostasis. *Nat Rev Immunol* 2006; 6:261–70.
  - 231 Reina-San-Martin B, Nussenzweig MC, Nussenzweig A, Difilippantonio S. Genomic instability, endoreduplication, and diminished Ig class-switch

- recombination in B cells lacking Nbs1. *Proc Natl Acad Sci U S A* 2005; **102**:1590–5.
- 232 Barnes KC, Neely JD, Duffy DL, Freidhoff LR, Breazeale DR, Schou C *et al.* Linkage of asthma and total serum IgE concentration to markers on chromosome 12q: evidence from Afro-Caribbean and Caucasian populations. *Genomics* 1996; **37**: 41–50.
- 233 Nickel R, Wahn U, Hizawa N, Maestri N, Duffy DL, Barnes KC *et al.* Evidence for linkage of chromosome 12q15–q24.1 markers to high total serum IgE concentrations in children of the German multicenter allergy study. *Genomics* 1997; **46**:159–62.
- 234 Wjst M, Fischer G, Immervoll T, Jung M, Saar K, Rueschendorf F *et al.* A genome-wide search for linkage to asthma. German Asthma Genetics Group. *Genomics* 1999; **58**:1–8.
- 235 Barnes KC, Freidhoff LR, Nickel R, Chiu YF, Juo SH, Hizawa N *et al.* Dense mapping of chromosome 12q13.12–q23.3 and linkage to asthma and atopy. *J Allergy Clin Immunol* 1999; **104**:485–91.
- 236 Schedel M, Carr D, Klopp N, Woitsch B, Illig T, Stachel D *et al.* A signal transducer and activator of transcription 6 haplotype influences the regulation of serum IgE levels. *J Allergy Clin Immunol* 2004; **114**:1100–5.
- 237 Weidinger S, Klopp N, Wagenpfeil S, Rummler L, Schedel M, Kabesch M *et al.* Association of a STAT 6 haplotype with elevated serum IgE levels in a population based cohort of white adults. *J Med Genet* 2004; **41**:658–63.
- 238 Duetsch G, Illig T, Loesgen S, Rohde K, Klopp N, Herbon N *et al.* STAT6 as an asthma candidate gene: polymorphism-screening, association and haplotype analysis in a Caucasian sib-pair study. *Hum Mol Genet* 2002; **11**:613–21.
- 239 Schedel M, Frei R, Bieli C, Cameron L, Adamski J, Lauener R *et al.* An IgE-associated polymorphism in STAT6 alters NF-kappaB binding, STAT6 promoter activity, and mRNA expression. *J Allergy Clin Immunol* 2009; **124**:583–9.
- 240 Daniels SE, Bhattacharya S, James A, Leaves NI, Young A, Hill MR *et al.* A genome-wide search for quantitative trait loci underlying asthma. *Nature* 1996; **383**:247–50.
- 241 Hizawa N, Freidhoff LR, Chiu YF, Ehrlich E, Luehr CA, Anderson JL *et al.* Genetic regulation of Dermatophagoides pteronyssinus-specific IgE responsiveness: a genome-wide multi-point linkage analysis in families recruited through 2 asthmatic sibs. Collaborative study on the genetics of asthma (CSGA). *J Allergy Clin Immunol* 1998; **102**:436–42.
- 242 Ulbrecht M, Eisenhut T, Bonisch J, Kruse R, Wjst M, Heinrich J *et al.* High serum IgE concentrations: association with HLA-DR and markers on chromosome 5q31 and chromosome 11q13. *J Allergy Clin Immunol* 1997; **99**:828–36.
- 243 Cardaba B, Moffatt MF, Fernandez E, Jurado A, Rojo M, Garcia M *et al.* Allergy to dermatophagoides in a group of Spanish gypsies: genetic restrictions. *Int Arch Allergy Immunol* 2001; **125**:297–306.
- 244 Mansur AH, Williams GA, Bishop DT, Markham AF, Lewis S, Britton J *et al.* Evidence for a role of HLA DRB1 alleles in the control of IgE levels, strengthened by interacting TCR A/D marker alleles. *Clin Exp Allergy* 2000; **30**:1371–8.
- 245 Woszczek G, Kowalski ML, Borowiec M. Association of asthma and total IgE levels with human leucocyte antigen-DR in patients with grass allergy. *Eur Respir J* 2002; **20**:79–85.
- 246 Moffatt MF, Schou C, Faux JA, Abecasis GR, James A, Musk AW *et al.* Association between quantitative traits underlying asthma and the HLA-DRB1 locus in a family-based population sample. *Eur J Hum Genet* 2001; **9**:341–6.
- 247 Germain RN. MHC-dependent antigen processing and peptide presentation: providing ligands for T lymphocyte activation. *Cell* 1994; **76**:287–99.
- 248 Jones EY, Fugger L, Strominger JL, Siebold C. MHC class II proteins and disease: a structural perspective. *Nat Rev Immunol* 2006; **6**:271–82.
- 249 Trowsdale J. The MHC, disease and selection. *Immunol Lett* 2011; **137**: 1–8.
- 250 Oshiba A, Hamelmann E, Haczku A, Takeda K, Conrad DH, Kikutani H *et al.* Modulation of antigen-induced B and T cell responses by antigen-specific IgE antibodies. *J Immunol* 1997; **159**:4056–63.
- 251 Mudde GC, Reischul IG, Corvaia N, Hren A, Poellabauer EM. Antigen presentation in allergic sensitization. *Immunol Cell Biol* 1996; **74**:167–73.
- 252 Holm J, Willumsen N, Wurtzen PA, Christensen LH, Lund K. Facilitated antigen presentation and its inhibition by blocking IgG antibodies depends on IgE repertoire complexity. *J Allergy Clin Immunol* 2011; **127**:1029–37.
- 253 Woitsch B, Carr D, Stachel D, Schmid I, Weiland SK, Fritzsch C *et al.* A comprehensive analysis of interleukin-4 receptor polymorphisms and their association with atopy and IgE regulation in childhood. *Int Arch Allergy Immunol* 2004; **135**:319–24.
- 254 Bottini N, Borgiani P, Otsu A, Saccucci P, Stefanini L, Greco E *et al.* IL-4 receptor alpha chain genetic polymorphism and total IgE levels in the English population: two-locus haplotypes are more informative than individual SNPs. *Clin Genet* 2002; **61**:288–92.
- 255 Mitsuyasu H, Yanagihara Y, Mao XQ, Gao PS, Arinobu Y, Ihara K *et al.* Cutting edge: dominant effect of Ile50Val variant of the human IL-4 receptor alpha-chain in IgE synthesis. *J Immunol* 1999; **162**:1227–31.
- 256 Izuohara K, Yanagihara Y, Hamasaki N, Shirakawa T, Hopkin JM. Atopy and the human IL-4 receptor alpha chain. *J Allergy Clin Immunol* 2000; **106**:S65–71.
- 257 Heinzmann A, Mao XQ, Akaiwa M, Kreomer RT, Gao PS, Ohshima K *et al.* Genetic variants of IL-13 signalling and human asthma and atopy. *Hum Mol Genet* 2000; **9**:549–59.
- 258 Kauppi P, Lindblad-Toh K, Sevón P, Toivonen HT, Rioux JD, Villapakkam A *et al.* A second-generation association study of the 5q31 cytokine gene cluster and the interleukin-4 receptor in asthma. *Genomics* 2001; **77**:35–42.
- 259 Risma KA, Wang N, Andrews RP, Cunningham CM, Ericksen MB, Bernstein JA *et al.* V75R576 IL-4 receptor alpha is associated with allergic asthma and enhanced IL-4 receptor function. *J Immunol* 2002; **169**:1604–10.
- 260 Leonard WJ, Zeng R, Spolski R. Interleukin 21: a cytokine/cytokine receptor system that has come of age. *J Leukoc Biol* 2008; **84**:348–56.

- 261 Mehta DS, Wurster AL, Grusby MJ. Biology of IL-21 and the IL-21 receptor. *Immunol Rev* 2004; **202**:84–95.
- 262 Konforte D, Simard N, Paige CJ. IL-21: an executor of B cell fate. *J Immunol* 2009; **182**:1781–7.
- 263 Suto A, Nakajima H, Hirose K, Suzuki K, Kagami S, Seto Y *et al.* Interleukin 21 prevents antigen-induced IgE production by inhibiting germ line C (epsilon) transcription of IL-4-stimulated B cells. *Blood* 2002; **100**:4565–73.
- 264 Ozaki K, Spolski R, Feng CG, Qi CF, Cheng J, Sher A *et al.* A critical role for IL-21 in regulating immunoglobulin production. *Science* 2002; **298**:1630–4.
- 265 Avery DT, Ma CS, Bryant VL, Santner-Nanan B, Nanan R, Wong M *et al.* STAT3 is required for IL-21-induced secretion of IgE from human naive B cells. *Blood* 2008; **112**:1784–93.
- 266 Caven TH, Sturgill JL, Conrad DH. BCR ligation antagonizes the IL-21 enhancement of anti-CD40/IL-4 plasma cell differentiation and IgE production found in low density human B cell cultures. *Cell Immunol* 2007; **247**:49–58.
- 267 Wood N, Bourque K, Donaldson DD, Collins M, Vercelli D, Goldman SJ *et al.* IL-21 effects on human IgE production in response to IL-4 or IL-13. *Cell Immunol* 2004; **231**:133–45.
- 268 Pene J, Guglielmi L, Gauchat JF, Harter N, Woisetschlager M, Boulay V *et al.* IFN-gamma-mediated inhibition of human IgE synthesis by IL-21 is associated with a polymorphism in the IL-21R gene. *J Immunol* 2006; **177**:5006–13.
- 269 Hecker M, Bohnert A, Konig IR, Bein G, Hackstein H. Novel genetic variation of human interleukin-21 receptor is associated with elevated IgE levels in females. *Genes Immun* 2003; **4**:228–33.
- 270 Kabesch M. Novel asthma-associated genes from genome-wide association studies: what is their significance? *Chest* 2010; **137**:909–15.
- 271 Weidinger S, Baurecht H, Naumann A, Novak N. Genome-wide association studies on IgE regulation: are genetics of IgE also genetics of atopic disease? *Curr Opin Allergy Clin Immunol* 2010; **10**:408–17.
- 272 Niwa Y, Potaczek DP, Kanada S, Takagi A, Shimokawa N, Ito T *et al.* FcepsilonRIalpha gene (FCER1A) promoter polymorphisms and total serum IgE levels in Japanese atopic dermatitis patients. *Int J Immunogenet* 2010; **37**:139–41.
- 273 Park KY, Park MK, Kim EJ, Lee MK, Seo SJ. FcepsilonRI gene promoter polymorphisms and total IgE levels in susceptibility to atopic dermatitis in Korea. *J Korean Med Sci* 2011; **26**:870–4.
- 274 Zhang Y, Duan S, Lin X, Zhang W, Meng N, Zhao L *et al.* SNPs in the FCER1A gene region show no association with allergic rhinitis in a Han Chinese population. *PLoS ONE* 2010; **5**:e15792.
- 275 Castro-Giner F, Bustamante M, Ramon Gonzalez J, Kogevinas M, Jarvis D, Heinrich J *et al.* A pooling-based genome-wide analysis identifies new potential candidate genes for atopy in the European community respiratory health survey (ECRHS). *BMC Med Genet* 2009; **10**:128.
- 276 Wan YI, Strachan DP, Evans DM, Henderson J, McKeever T, Holloway JW *et al.* A genome-wide association study to identify genetic determinants of atopy in subjects from the United Kingdom. *J Allergy Clin Immunol* 2011; **127**:223–31.
- 277 Andiappan AK, Wang de Y, Anantharaman R, Parate PN, Suri BK, Low HQ *et al.* Genome-wide association study for atopy and allergic rhinitis in a Singapore Chinese population. *PLoS ONE* 2011; **6**:e19719.
- 278 Ramasamy A, Curjuric I, Coin LJ, Kumar A, McArdle WL, Imboden M *et al.* A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. *J Allergy Clin Immunol* 2011; **128**:996–1005.
- 279 Esparza-Gordillo J, Weidinger S, Folster-Holst R, Bauerfeind A, Ruschen-dorf F, Patone G *et al.* A common variant on chromosome 11q13 is associated with atopic dermatitis. *Nat Genet* 2009; **41**:596–601.
- 280 <http://www.ncrna.org/idiographica/>.
- 281 Kin T, Ono Y. Idiographica: a general-purpose web application to build idiograms on-demand for human, mouse and rat. *Bioinformatics* 2007; **23**:2945–6.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. (A) References underlying Fig. 3 (GWAS part); (B) references underlying Fig. 3 (linkage part); (C) references underlying Fig. 4.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

| A. Total serum IgE susceptibility loci identified by GWAS-based studies |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Locus                                                                   | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>1q23</b>                                                             | <p><a href="#">Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus.</a></p> <p>Weidinger S, Gieger C, Rodriguez E, Baurecht H, Mempel M, Klopp N, et al.<br/>PLoS Genet. 2008 Aug;4(8):e1000166. Epub 2008 Aug 22.</p> <p><i>and</i></p> <p><a href="#">A large-scale, consortium-based genomewide association study of asthma.</a></p> <p>Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al.<br/>N Engl J Med. 2010 Sep 23;363(13):1211-21.</p> <p><i>and</i></p> <p><a href="#">A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study.</a></p> <p>Granada M, Wilk JB, Tuzova M, Strachan DP, Weidinger S, Albrecht E, et al<br/>J Allergy Clin Immunol. 2011 Nov 8. [Epub ahead of print]</p> |
| Locus                                                                   | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>5q31</b>                                                             | <p><a href="#">Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus.</a></p> <p>Weidinger S, Gieger C, Rodriguez E, Baurecht H, Mempel M, Klopp N, et al.<br/>PLoS Genet. 2008 Aug;4(8):e1000166. Epub 2008 Aug 22.</p> <p><i>and</i></p> <p><a href="#">A large-scale, consortium-based genomewide association study of asthma.</a></p> <p>Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al.<br/>N Engl J Med. 2010 Sep 23;363(13):1211-21.</p> <p><i>and</i></p> <p><a href="#">A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study.</a></p> <p>Granada M, Wilk JB, Tuzova M, Strachan DP, Weidinger S, Albrecht E, et al<br/>J Allergy Clin Immunol. 2011 Nov 8. [Epub ahead of print]</p> |
| Locus                                                                   | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>12q13</b>                                                            | <p><a href="#">Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus.</a></p> <p>Weidinger S, Gieger C, Rodriguez E, Baurecht H, Mempel M, Klopp N, et al.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               | <p>PLoS Genet. 2008 Aug;4(8):e1000166. Epub 2008 Aug 22.</p> <p><i>and</i></p> <p><a href="#">A large-scale, consortium-based genomewide association study of asthma.</a></p> <p>Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al.<br/>N Engl J Med. 2010 Sep 23;363(13):1211-21.</p> <p><i>and</i></p> <p><a href="#">A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study.</a></p> <p>Granada M, Wilk JB, Tuzova M, Strachan DP, Weidinger S, Albrecht E, et al<br/>J Allergy Clin Immunol. 2011 Nov 8. [Epub ahead of print]</p> |
| Locus         | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>6p21.3</b> | <p><a href="#">A large-scale, consortium-based genomewide association study of asthma.</a></p> <p>Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al.<br/>N Engl J Med. 2010 Sep 23;363(13):1211-21.</p> <p><i>and</i></p> <p><a href="#">A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study.</a></p> <p>Granada M, Wilk JB, Tuzova M, Strachan DP, Weidinger S, Albrecht E, et al<br/>J Allergy Clin Immunol. 2011 Nov 8. [Epub ahead of print]</p>                                                                                |
| Locus         | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>16p12</b>  | <p><a href="#">A large-scale, consortium-based genomewide association study of asthma.</a></p> <p>Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al.<br/>N Engl J Med. 2010 Sep 23;363(13):1211-21.</p>                                                                                                                                                                                                                                                                                                                                                                          |

| B. Loci shown to be linked to total serum IgE levels in studies comprising at least 500 genotyped participants**†                     |                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Locus/-i                                                                                                                              | References                                                                                                                                                                                                                                                                                           |
| <b>12q24.3</b><br><b>13q14.2</b>                                                                                                      | <a href="#">Chromosome 12q24.3 controls sensitization to cat allergen in patients with asthma from Siberia, Russia.</a><br>Gusareva ES, Bragina EJ, Buinova SN, Chernyak BA, Puzyrev VP, Ogorodova LM, et al.<br>Immunol Lett. 2009 Jun 30;125(1):1-6. Epub 2009 May 18.                             |
| Locus/-i                                                                                                                              | References                                                                                                                                                                                                                                                                                           |
| <b>7p15</b><br><b>20p12</b><br><b>17q12</b><br><b>3q21</b><br><b>7p21</b>                                                             | <a href="#">Sex-specific linkage to total serum immunoglobulin E in families of children with asthma in Costa Rica.</a><br>Raby BA, Soto-Quiros ME, Avila L, Lake SL, Murphy A, Liang C, et al.<br>Hum Mol Genet. 2007 Feb 1;16(3):243-53. Epub 2006 Dec 1.                                          |
| Locus/-i                                                                                                                              | References                                                                                                                                                                                                                                                                                           |
| <b>1q23.1</b><br><b>5q31.3-5q33.3</b><br><b>8q21</b>                                                                                  | <a href="#">Quantitative linkage genome scan for atopy in a large collection of Caucasian families.</a><br>Webb BT, van den Oord E, Akkari A, Wilton S, Ly T, Duff R, et al.<br>Hum Genet. 2007 Mar;121(1):83-92. Epub 2006 Nov 14.                                                                  |
| Locus/-i                                                                                                                              | References                                                                                                                                                                                                                                                                                           |
| <b>1p36.12-1p34.3</b><br><b>1q23.3-1q32.1</b><br><b>7p14.2-7p12.3</b><br><b>7q11.21-7q21.11</b><br><b>11p15.5-p13</b><br><b>11q25</b> | <a href="#">Phenotypic and genetic heterogeneity in a genome-wide linkage study of asthma families.</a><br>Altmüller J, Seidel C, Lee YA, Loesgen S, Bulle D, Friedrichs F, et al.<br>BMC Pulm Med. 2005 Jan 5;5:1.                                                                                  |
| Locus/-i                                                                                                                              | References                                                                                                                                                                                                                                                                                           |
| <b>12p13</b>                                                                                                                          | <a href="#">Clustering patterns of LOD scores for asthma-related phenotypes revealed by a genome-wide screen in 295 French EGEA families.</a><br>Bouzigon E, Dizier MH, Krähenbühl C, Lemaître A, Annesi-Maesano I, Betard C, et al.<br>Hum Mol Genet. 2004 Dec 15;13(24):3103-13. Epub 2004 Oct 27. |
| Locus/-i                                                                                                                              | References                                                                                                                                                                                                                                                                                           |
| <b>1q31.1</b>                                                                                                                         | <a href="#">A genomewide search for quantitative-trait loci underlying asthma.</a>                                                                                                                                                                                                                   |

Xu X, Fang Z, Wang B, Chen C, Guang W, Jin Y, et al.

Am J Hum Genet. 2001 Dec;69(6):1271-7. Epub 2001 Oct 22. Erratum in: Am J Hum Genet 2002 Jul;71(1):215.

| Locus/-i                                                                                         | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>19q13.3</b><br><b>19p13.3</b>                                                                 | <a href="#">Linkage to atopy on chromosome 19 in north-eastern Italian families with allergic asthma.</a><br>Venanzi S, Malerba G, Galavotti R, Lauciello MC, Trabetti E, Zanoni G, et al.<br>Clin Exp Allergy. 2001 Aug;31(8):1220-4.<br><br><i>and/or</i><br><br><a href="#">Candidate genes and a genome-wide search in Italian families with atopic asthmatic children.</a><br>Malerba G, Trabetti E, Patuzzo C, Lauciello MC, Galavotti R, Pescollderungg L, et al.<br>Clin Exp Allergy. 1999 Dec;29 Suppl 4:27-30. |
| Locus/-i                                                                                         | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>7p14-7p15</b>                                                                                 | <a href="#">A susceptibility locus for asthma-related traits on chromosome 7 revealed by genome-wide scan in a founder population.</a><br>Laitinen T, Daly MJ, Rioux JD, Kauppi P, Laprise C, Petäys T, et al.<br>Nat Genet. 2001 May;28(1):87-91.                                                                                                                                                                                                                                                                       |
| Locus/-i                                                                                         | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>4q34.1</b><br><b>2q22.1</b><br><b>4p13</b><br><b>18q23</b><br><b>9q31.1</b><br><b>12p13.2</b> | <a href="#">Genome-wide linkage analyses of total serum IgE using variance components analysis in asthmatic families.</a><br>Mathias RA, Freidhoff LR, Blumenthal MN, Meyers DA, Lester L, King R, et al.<br>Genet Epidemiol. 2001 Apr;20(3):340-55.                                                                                                                                                                                                                                                                     |
| Locus/-i                                                                                         | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>5q23-(5q31)-5q33</b><br><b>7q11-7q22</b><br><b>12q23-12q24</b>                                | <a href="#">Genome-wide search for atopy susceptibility genes in Dutch families with asthma.</a><br>Koppelman GH, Stine OC, Xu J, Howard TD, Zheng SL, Kauffman HF, et al.<br>J Allergy Clin Immunol. 2002 Mar;109(3):498-506.<br><br><i>and/or</i><br><br><a href="#">Major genes regulating total serum immunoglobulin E levels in families with asthma.</a><br>Xu J, Postma DS, Howard TD, Koppelman GH, Zheng SL, Stine OC, et al.                                                                                   |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | <p>Am J Hum Genet. 2000 Nov;67(5):1163-73. Epub 2000 Oct 6.</p> <p><i>and/or</i></p> <p><a href="#">Susceptibility loci regulating total serum IgE levels, bronchial hyperresponsiveness, and clinical asthma map to chromosome 5q.</a></p> <p>Amelung PJ, Postma D, Panhuysen CI, Meyers DA, Bleecker ER.<br/>Chest. 1997 Jun;111(6 Suppl):77S-78S. No abstract available.</p> <p><i>and/or</i></p> <p><a href="#">Evidence for linkage of total serum IgE and bronchial hyperresponsiveness to chromosome 5q: a major regulatory locus important in asthma.</a></p> <p>Bleecker ER, Amelung PJ, Levitt RC, Postma DS, Meyers DA.<br/>Clin Exp Allergy. 1995 Nov;25 Suppl 2:84-8; discussion 95-6. No abstract available.</p> |
| Locus/-i             | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>5q31-33</b>       | <p><a href="#">Indication of linkage of serum IgE levels to the interleukin-4 gene and exclusion of the contribution of the (-590 C to T) interleukin-4 promoter polymorphism to IgE variation.</a></p> <p>Dizier MH, Sandford A, Walley A, Philippi A, Cookson W, Demenais F.<br/>Genet Epidemiol. 1999;16(1):84-94.</p> <p><i>and/or</i></p> <p><a href="#">Linkage of chromosome 5q and 11q gene markers to asthma-associated quantitative traits in Australian children.</a></p> <p>Palmer LJ, Daniels SE, Rye PJ, Gibson NA, Tay GK, Cookson WO, et al.<br/>Am J Respir Crit Care Med. 1998 Dec;158(6):1825-30.</p>                                                                                                       |
| Locus/-i             | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>12q15-12q24.1</b> | <p><a href="#">Testing for gene-gene interaction controlling total IgE in families from Barbados: evidence of sensitivity regarding linkage heterogeneity among families.</a></p> <p>Barnes KC, Mathias RA, Nickel R, Freidhoff LR, Stockton ML, Xue X, et al.<br/>Genomics. 2001 Jan 15;71(2):246-51.</p> <p><i>and/or</i></p> <p><a href="#">Linkage of asthma and total serum IgE concentration to markers on chromosome 12q: evidence from Afro-Caribbean and</a></p>                                                                                                                                                                                                                                                      |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Caucasian populations.</a><br>Barnes KC, Neely JD, Duffy DL, Freidhoff LR, Breazeale DR, Schou C, et al.<br>Genomics. 1996 Oct 1;37(1):41-50.                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                     |
| Locus/-i                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | References                                                                                                                                                                                                          |
| <b>14q11.2</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <a href="#">Genetic linkage of T-cell receptor alpha/delta complex to specific IgE responses.</a><br>Moffatt MF, Hill MR, Cornélis F, Schou C, Faux JA, Young RP, et al.<br>Lancet. 1994 Jun 25;343(8913):1597-600. |
| <p>*Chromosomal band locations accroding to what has been stated by the Authors of respective papers. If no detail chromosomal band location had been available from the paper, the mapping of the reported genetic markers was conducted by D. Potaczek using ENSEMBL (<a href="http://www.ensembl.org/index.html">http://www.ensembl.org/index.html</a>).</p> <p>†Reviews, meta-analyses of already published data, and GWAS-based studies were not taken into account in the present search.</p> |                                                                                                                                                                                                                     |

**C. Genes shown to be associated with total serum IgE levels in more than three independent studies comprising at least 500 genotyped participants each\***

|          |                                                                                                                            |                                                                                                                                                                                                                                                                                        |                           |
|----------|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Gene:    | <b>ADAM33</b> (ADAM metallopeptidase domain 33; a disintegrin and metalloprotease domain 33)                               |                                                                                                                                                                                                                                                                                        | Chr. <b>20p13</b>         |
| Studies: | 1.                                                                                                                         | <a href="#">A Six-SNP haplotype of ADAM33 is associated with asthma in a population of Cartagena, Colombia.</a><br>Vergara CI, Acevedo N, Jiménez S, Martínez B, Mercado D, Gusmão L, et al.<br>Int Arch Allergy Immunol. 2010;152(1):32-40. Epub 2009 Nov 24.                         |                           |
|          | 2.                                                                                                                         | <a href="#">Asthma is associated with single-nucleotide polymorphisms in ADAM33.</a><br>Werner M, Herbon N, Gohlke H, Altmüller J, Knapp M, Heinrich J, et al.<br>Clin Exp Allergy. 2004 Jan;34(1):26-31.                                                                              |                           |
|          | 3.                                                                                                                         | <a href="#">Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations.</a><br>Howard TD, Postma DS, Jongepier H, Moore WC, Koppelman GH, Zheng SL, et al.<br>J Allergy Clin Immunol. 2003 Oct;112(4):717-22.                     |                           |
|          |                                                                                                                            |                                                                                                                                                                                                                                                                                        |                           |
| Gene:    | <b>CCL11</b> [chemokine (C-C motif) ligand 11; C-C motif chemokine 11; eosinophil chemotactic protein; eotaxin; eotaxin-1] |                                                                                                                                                                                                                                                                                        | Chr. <b>17q21.1-q21.2</b> |
| Studies: | 1.                                                                                                                         | <a href="#">A hexanucleotide repeat upstream of eotaxin gene promoter is associated with asthma, serum total IgE and plasma eotaxin levels.</a><br>Batra J, Rajpoot R, Ahluwalia J, Devarapu SK, Sharma SK, Dinda AK, et al.<br>J Med Genet. 2007 Jun;44(6):397-403. Epub 2007 Jan 12. |                           |
|          | 2.                                                                                                                         | <a href="#">Eotaxin polymorphisms and serum total IgE levels in children with asthma.</a><br>Raby BA, Van Steen K, Lazarus R, Celedón JC, Silverman EK, Weiss ST.<br>J Allergy Clin Immunol. 2006 Feb;117(2):298-305.                                                                  |                           |
|          | 3.                                                                                                                         | <a href="#">Association of Eotaxin gene family with asthma and serum total IgE.</a><br>Shin HD, Kim LH, Park BL, Jung JH, Kim JY, Chung IY, et al.<br>Hum Mol Genet. 2003 Jun 1;12(11):1279-85. Erratum in: Hum Mol Genet. 2003 Aug 15;12(16):2083.                                    |                           |
|          |                                                                                                                            |                                                                                                                                                                                                                                                                                        |                           |

|          |                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                    |
|----------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Gene:    | <b>CD14 (monocyte differentiation antigen CD14)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Chr. <b>5q31.1</b> |
| Studies: | 1.                                                  | <p><a href="#">Toll-like receptors and microbial exposure: gene-gene and gene-environment interaction in the development of atopy.</a><br/> Reijmerink NE, Kerkhof M, Bottema RW, Gerritsen J, Stelma FF, Thijs C, et al.<br/> Eur Respir J. 2011 Feb 24. [Epub ahead of print]</p> <p>or</p> <p><a href="#">Interleukin 13, CD14, pet and tobacco smoke influence atopy in three Dutch cohorts: the allergenic study.</a><br/> Bottema RW, Reijmerink NE, Kerkhof M, Koppelman GH, Stelma FF, Gerritsen J, et al.<br/> Eur Respir J. 2008 Sep;32(3):593-602. Epub 2008 Apr 16.</p> |                    |
|          | 2.                                                  | <p><a href="#">Analysis of -675 4 g/5 G SERPINE1 and C-159T CD14 polymorphisms in house dust mite-allergic asthma patients.</a><br/> Kowal K, Bodzenta-Lukaszyk A, Pampuch A, Szmitkowski M, Zukowski S, Donati MB, et al.<br/> J Investig Allergol Clin Immunol. 2008;18(4):284-92.</p>                                                                                                                                                                                                                                                                                            |                    |
|          | 3.                                                  | <p><a href="#">Gene-environment interactions with CD14 C-260T and their relationship to total serum IgE levels in adults.</a><br/> Williams LK, McPhee RA, Ownby DR, Peterson EL, James M, Zoratti EM, et al.<br/> J Allergy Clin Immunol. 2006 Oct;118(4):851-7. Epub 2006 Aug 30.</p>                                                                                                                                                                                                                                                                                             |                    |
|          | 4.                                                  | <p><a href="#">The effect of polymorphisms at the CD14 promoter and the TLR4 gene on asthma phenotypes in Turkish children with asthma.</a><br/> Saçkesen C, Karaaslan C, Keskin O, Tokol N, Tahan F, Civelek E, et al.<br/> Allergy. 2005 Dec;60(12):1485-92.</p>                                                                                                                                                                                                                                                                                                                  |                    |
|          | 5.                                                  | <p><a href="#">Opposite effects of CD 14/-260 on serum IgE levels in children raised in different environments.</a><br/> Eder W, Klimecki W, Yu L, von Mutius E, Riedler J, Braun-Fahrlander C, et al.<br/> J Allergy Clin Immunol. 2005 Sep;116(3):601-7.</p>                                                                                                                                                                                                                                                                                                                      |                    |
|          | 6.                                                  | <p><a href="#">Suggestive evidence of association of C-159T functional polymorphism of the CD14 gene with atopic asthma in northern and northwestern Indian populations.</a><br/> Sharma M, Batra J, Mabalirajan U, Goswami S, Ganguly D, Lahkar B, et al.<br/> Immunogenetics. 2004 Oct;56(7):544-7. Epub 2004 Sep 18.</p>                                                                                                                                                                                                                                                         |                    |
|          | 7.                                                  | <p><a href="#">Serum total IgE levels and CD14 on chromosome 5q31.</a><br/> Gao PS, Mao XQ, Baldini M, Roberts MH, Adra CN, Shirakawa T, et al.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                 |                    |

|          |                                                            |                                                                                                                                                                                                                                                                                                  |
|----------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          |                                                            | Clin Genet. 1999 Aug;56(2):164-5. No abstract available.                                                                                                                                                                                                                                         |
| Gene:    | <b>CTLA4 (cytotoxic T-lymphocyte-associated protein 4)</b> |                                                                                                                                                                                                                                                                                                  |
|          |                                                            | Chr. <b>2q33</b>                                                                                                                                                                                                                                                                                 |
| Studies: | 1.                                                         | <a href="#">Cytotoxic T lymphocyte-associated antigen-4 gene polymorphisms confer susceptibility to atopic asthma in Korean children.</a><br>Sohn MH, Kim SH, Song TW, Kim KW, Kim ES, Park HS, et al.<br>Pediatr Pulmonol. 2007 Jun;42(6):542-7.                                                |
|          | 2.                                                         | <a href="#">CTLA-4 polymorphisms in allergy and asthma and the TH1/ TH2 paradigm.</a><br>Munthe-Kaas MC, Carlsen KH, Helms PJ, Gerritsen J, Whyte M, Feijen M, et al.<br>J Allergy Clin Immunol. 2004 Aug;114(2):280-7.                                                                          |
|          | 3.                                                         | <a href="#">Polymorphism of the immune-braking gene CTLA-4 (+49) involved in gender discrepancy of serum total IgE levels and allergic diseases.</a><br>Yang KD, Liu CA, Chang JC, Chuang H, Ou CY, Hsu TY, et al.<br>Clin Exp Allergy. 2004 Jan;34(1):32-7.                                     |
|          | 4.                                                         | <a href="#">Increased total serum IgE levels in patients with asthma and promoter polymorphisms at CTLA4 and FCER1B.</a><br>Hizawa N, Yamaguchi E, Jinushi E, Konno S, Kawakami Y, Nishimura M.<br>J Allergy Clin Immunol. 2001 Jul;108(1):74-9.                                                 |
| Gene:    | <b>IL4 (interleukin 4; interleukin-4)</b>                  |                                                                                                                                                                                                                                                                                                  |
|          |                                                            | Chr. <b>5q31.1</b>                                                                                                                                                                                                                                                                               |
| Studies: | 1.                                                         | <a href="#">A comprehensive evaluation of IL4 variants in ethnically diverse populations: association of total serum IgE levels and asthma in white subjects.</a><br>Basehore MJ, Howard TD, Lange LA, Moore WC, Hawkins GA, Marshik PL, et al.<br>J Allergy Clin Immunol. 2004 Jul;114(1):80-7. |
|          | 2.                                                         | <a href="#">IL4-589C/T polymorphism and IgE levels in severe malaria.</a><br>Verra F, Luoni G, Calissano C, Troye-Blomberg M, Perlmann P, Perlmann H, et al.<br>Acta Trop. 2004 Apr;90(2):205-9.                                                                                                 |
|          | 3.                                                         | <a href="#">A complete screening of the IL4 gene: novel polymorphisms and their association with asthma and IgE in childhood.</a><br>Kabesch M, Tzotcheva I, Carr D, Höfler C, Weiland SK, Fritzsche C, et al.                                                                                   |

|          |                                                                                                                           |                                                                                                                                                                                                                                                                                                      |
|----------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          |                                                                                                                           | J Allergy Clin Immunol. 2003 Nov;112(5):893-8.                                                                                                                                                                                                                                                       |
|          |                                                                                                                           |                                                                                                                                                                                                                                                                                                      |
| Gene:    | <b><i>IL4R</i> (interleukin-4 receptor; IL-4 receptor subunit alpha; IL-4R subunit alpha; IL-4R-alpha; <i>IL-4RA</i>)</b> |                                                                                                                                                                                                                                                                                                      |
|          |                                                                                                                           | Chr. <b>16p12.1-p11.2</b>                                                                                                                                                                                                                                                                            |
| Studies: | 1.                                                                                                                        | <a href="#">A multi-centre study of candidate genes for wheeze and allergy: the International Study of Asthma and Allergies in Childhood Phase 2.</a><br>Genuneit J, Cantelmo JL, Weinmayr G, Wong GW, Cooper PJ, Riikj rv MA, et al.<br>Clin Exp Allergy. 2009 Dec;39(12):1875-88.                  |
|          | 2.                                                                                                                        | <a href="#">IL-4 receptor genetic polymorphisms and asthma in Asian populations.</a><br>Zhang W, Zhang X, Qiu D, Sandford A, Tan WC.<br>Respir Med. 2007 Jan;101(1):186-90. Epub 2006 Jun 6.                                                                                                         |
|          | 3.                                                                                                                        | <a href="#">Association of IL13 with total IgE: evidence against an inverse association of atopy and diabetes.</a><br>Maier LM, Howson JM, Walker N, Spickett GP, Jones RW, Ring SM, et al.<br>J Allergy Clin Immunol. 2006 Jun;117(6):1306-13. Epub 2006 Apr 3.                                     |
|          | 4.                                                                                                                        | <a href="#">Asthma families show transmission disequilibrium of gene variants in the vitamin D metabolism and signalling pathway.</a><br>Wjst M, Altm ller J, Faus-Kessler T, Braig C, Bahnweg M, Andr  E.<br>Respir Res. 2006 Apr 6;7:60.                                                           |
|          | 5.                                                                                                                        | <a href="#">A comprehensive analysis of interleukin-4 receptor polymorphisms and their association with atopy and IgE regulation in childhood.</a><br>Woitsch B, Carr D, Stachel D, Schmid I, Weiland SK, Fritzsche C, et al.<br>Int Arch Allergy Immunol. 2004 Dec;135(4):319-24. Epub 2004 Nov 24. |
|          | 6.                                                                                                                        | <a href="#">A second-generation association study of the 5q31 cytokine gene cluster and the interleukin-4 receptor in asthma.</a><br>Kauppi P, Lindblad-Toh K, Sevon P, Toivonen HT, Rioux JD, Villapakkam A, et al.<br>Genomics. 2001 Sep;77(1-2):35-42.                                            |
|          |                                                                                                                           |                                                                                                                                                                                                                                                                                                      |
| Gene:    | <b><i>IL10</i> (interleukin 10)</b>                                                                                       |                                                                                                                                                                                                                                                                                                      |
|          |                                                                                                                           | Chr. <b>1q31-q32</b>                                                                                                                                                                                                                                                                                 |
| Studies: | 1.                                                                                                                        | <a href="#">Polymorphisms in IL10 are associated with total Immunoglobulin E levels and Schistosoma mansoni infection intensity in a Brazilian population.</a>                                                                                                                                       |

|          |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          |                              | <p>Grant AV, Araujo MI, Ponte EV, Oliveira RR, Cruz AA, Barnes KC, et al.<br/>Genes Immun. 2011 Jan;12(1):46-50. Epub 2010 Oct 7.</p> <p>2. <a href="#">Gene-gene interaction in regulatory T-cell function in atopy and asthma development in childhood.</a><br/>Bottema RW, Kerkhof M, Reijmerink NE, Thijs C, Smit HA, van Schayck CP, et al.<br/>J Allergy Clin Immunol. 2010 Aug;126(2):338-46, 346.e1-10.</p> <p>3. <a href="#">Immunogenetic control of antibody responsiveness in a malaria endemic area.</a><br/>Carpenter D, Abushama H, Bereczky S, Färnert A, Rooth I, Troye-Blomberg M, et al.<br/>Hum Immunol. 2007 Mar;68(3):165-9. Epub 2006 Dec 28.</p> <p>4. <a href="#">Asthma families show transmission disequilibrium of gene variants in the vitamin D metabolism and signalling pathway.</a><br/>Wjst M, Altmüller J, Faus-Kessler T, Braig C, Bahnweg M, André E.<br/>Respir Res. 2006 Apr 6;7:60.</p> <p>5. <a href="#">Interleukin-10 gene promoter region polymorphism is associated with eosinophil count and circulating immunoglobulin E in adult asthma.</a><br/>Karjalainen J, Hulkkonen J, Nieminen MM, Huhtala H, Aromaa A, Klaukka T, et al.<br/>Clin Exp Allergy. 2003 Jan;33(1):78-83.</p> |
|          |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Gene:    | <b>IL13 (interleukin 13)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|          |                              | Chr. <b>5q31</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Studies: | 1.                           | <p><a href="#">Interleukin 13 and interleukin 4 receptor-α polymorphisms in rhinitis and asthma.</a><br/>Bottema RW, Nolte IM, Howard TD, Koppelman GH, Dubois AE, de Meer G, et al.<br/>Int Arch Allergy Immunol. 2010;153(3):259-67. Epub 2010 May 19.</p> <p>2. <a href="#">Birth order modifies the effect of IL13 gene polymorphisms on serum IgE at age 10 and skin prick test at ages 4, 10 and 18: a prospective birth cohort study.</a><br/>Ogbuanu IU, Karmaus WJ, Zhang H, Sabo-Attwood T, Ewart S, Roberts G, et al.<br/>Allergy Asthma Clin Immunol. 2010 Apr 20;6(1):6.</p> <p>3. <a href="#">A multi-centre study of candidate genes for wheeze and allergy: the International Study of Asthma and Allergies in Childhood Phase 2.</a><br/>Genuneit J, Cantelmo JL, Weinmayr G, Wong GW, Cooper PJ, Riiikjäv MA, et al.<br/>Clin Exp Allergy. 2009 Dec;39(12):1875-88.</p>                                                                                                                                                                                                                                                                                                                                        |

4. [Association of IL-13 polymorphisms with leukotriene receptor antagonist drug responsiveness in Korean children with exercise-induced bronchoconstriction.](#)  
Kang MJ, Lee SY, Kim HB, Yu J, Kim BJ, Choi WA, Jang SO, et al.  
Pharmacogenet Genomics. 2008 Jul;18(7):551-8.
5. [Interleukin 13, CD14, pet and tobacco smoke influence atopy in three Dutch cohorts: the allergenic study.](#)  
Bottema RW, Reijmerink NE, Kerkhof M, Koppelman GH, Stelma FF, Gerritsen J, et al.  
Eur Respir J. 2008 Sep;32(3):593-602. Epub 2008 Apr 16.
6. [Polymorphisms in IL13, total IgE, eosinophilia, and asthma exacerbations in childhood.](#)  
Hunninghake GM, Soto-Quirós ME, Avila L, Su J, Murphy A, Demeo DL, et al.  
J Allergy Clin Immunol. 2007 Jul;120(1):84-90. Epub 2007 Jun 11.
7. [Allergy-related polymorphisms influence glioma status and serum IgE levels.](#)  
Wiemels JL, Wiencke JK, Kelsey KT, Moghadassi M, Rice T, Urayama KY, et al.  
Cancer Epidemiol Biomarkers Prev. 2007 Jun;16(6):1229-35.
8. [Gene-gene interaction between IL-13 and IL-13Ralpha1 is associated with total IgE in Korean children with atopic asthma.](#)  
Kim HB, Lee YC, Lee SY, Jung J, Jin HS, Kim JH, et al.  
J Hum Genet. 2006;51(12):1055-62. Epub 2006 Sep 28.
9. [Association of IL13 with total IgE: evidence against an inverse association of atopy and diabetes.](#)  
Maier LM, Howson JM, Walker N, Spickett GP, Jones RW, Ring SM, et al.  
J Allergy Clin Immunol. 2006 Jun;117(6):1306-13. Epub 2006 Apr 3.
10. [Variation in conserved non-coding sequences on chromosome 5q and susceptibility to asthma and atopy.](#)  
Donfack J, Schneider DH, Tan Z, Kurz T, Dubchak I, Frazer KA, et al.  
Respir Res. 2005 Dec 10;6:145.
11. [Association study of the IL13 variant Arg110Gln in atopic diseases and juvenile idiopathic arthritis.](#)  
Heinzmann A, Jerkic SP, Ganter K, Kurz T, Blattmann S, Schuchmann L, et al.  
J Allergy Clin Immunol. 2003 Oct;112(4):735-9.
12. [Associations between total serum IgE levels and the 6 potentially functional variants within the genes IL4, IL13, and IL4RA in German](#)

|          |                                                                                                 |                                                                                                                                                                                                                                                                                                       |
|----------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          |                                                                                                 | <a href="#">children: the German Multicenter Atopy Study.</a><br>Liu X, Beaty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al.<br>J Allergy Clin Immunol. 2003 Aug;112(2):382-8.                                                                                                                   |
| 13.      |                                                                                                 | <a href="#">A second-generation association study of the 5q31 cytokine gene cluster and the interleukin-4 receptor in asthma.</a><br>Kauppi P, Lindblad-Toh K, Sevon P, Toivonen HT, Rioux JD, Villapakkam A, et al.<br>Genomics. 2001 Sep;77(1-2):35-42.                                             |
| 14.      |                                                                                                 | <a href="#">A cluster of seven tightly linked polymorphisms in the IL-13 gene is associated with total serum IgE levels in three populations of white children.</a><br>Graves PE, Kabesch M, Halonen M, Holberg CJ, Baldini M, Fritzsche C, et al.<br>J Allergy Clin Immunol. 2000 Mar;105(3):506-13. |
|          |                                                                                                 |                                                                                                                                                                                                                                                                                                       |
| Gene:    | <b>LTA (LT; TNFB; lymphotoxin alpha; tumor necrosis factor beta; TNF superfamily, member 1)</b> |                                                                                                                                                                                                                                                                                                       |
|          |                                                                                                 | Chr. <b>6p21.3</b>                                                                                                                                                                                                                                                                                    |
| Studies: | 1.                                                                                              | <a href="#">Association of TNF haplotypes with asthma, serum IgE levels, and correlation with serum TNF-alpha levels.</a><br>Sharma S, Sharma A, Kumar S, Sharma SK, Ghosh B.<br>Am J Respir Cell Mol Biol. 2006 Oct;35(4):488-95. Epub 2006 May 25.                                                  |
|          | 2.                                                                                              | <a href="#">Association of tumor necrosis factor polymorphisms with asthma and serum total IgE.</a><br>Shin HD, Park BL, Kim LH, Jung JH, Wang HJ, Kim YJ, et al.<br>Hum Mol Genet. 2004 Feb 15;13(4):397-403. Epub 2003 Dec 17.                                                                      |
|          | 3.                                                                                              | <a href="#">Association of a lymphotoxin alpha gene polymorphism and atopy in Italian families.</a><br>Trabetti E, Patuzzo C, Malerba G, Galavotti R, Martinati LC, Boner AL, et al.<br>J Med Genet. 1999 Apr;36(4):323-5.                                                                            |
|          |                                                                                                 | or                                                                                                                                                                                                                                                                                                    |
|          |                                                                                                 | <a href="#">Candidate genes and a genome-wide search in Italian families with atopic asthmatic children.</a><br>Malerba G, Trabetti E, Patuzzo C, Lauciello MC, Galavotti R, Pescollderung L, et al.<br>Clin Exp Allergy. 1999 Dec;29 Suppl 4:27-30.                                                  |

|          |                                                                                                                                              |                                                                                                                                                                                                                                                                                         |             |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Gene:    | <b>NOD2 (nucleotide-binding oligomerization domain containing 2; caspase recruitment domain 15; CARD15)</b>                                  |                                                                                                                                                                                                                                                                                         | Chr. 16q21  |
| Studies: | 1.                                                                                                                                           | <a href="#">TLR-related pathway analysis: novel gene-gene interactions in the development of asthma and atopy.</a><br>Reijmerink NE, Bottema RW, Kerkhof M, Gerritsen J, Stelma FF, Thijs C, et al.<br>Allergy. 2010 Feb;65(2):199-207. Epub 2009 Nov 25.                               |             |
|          | 2.                                                                                                                                           | <a href="#">Asthma families show transmission disequilibrium of gene variants in the vitamin D metabolism and signalling pathway.</a><br>Wjst M, Altmüller J, Faus-Kessler T, Braig C, Bahnweg M, André E.<br>Respir Res. 2006 Apr 6;7:60.                                              |             |
|          | 3.                                                                                                                                           | <a href="#">Association of CARD15 polymorphisms with atopy-related traits in a population-based cohort of Caucasian adults.</a><br>Weidinger S, Klopp N, Rummeler L, Wagenpfeil S, Baurecht HJ, Gauger A, et al.<br>Clin Exp Allergy. 2005 Jul;35(7):866-72.                            |             |
|          | 4.                                                                                                                                           | <a href="#">Association between polymorphisms in caspase recruitment domain containing protein 15 and allergy in two German populations.</a><br>Kabesch M, Peters W, Carr D, Leupold W, Weiland SK, von Mutius E.<br>J Allergy Clin Immunol. 2003 Apr;111(4):813-7.                     |             |
|          |                                                                                                                                              |                                                                                                                                                                                                                                                                                         |             |
| Gene:    | <b>NSPR1 (neuropeptide S receptor 1; G protein-coupled receptor 154; G protein-coupled receptor for asthma susceptibility; GPRA; GPR154)</b> |                                                                                                                                                                                                                                                                                         | Chr. 7p14.3 |
| Studies: | 1.                                                                                                                                           | <a href="#">Association of G-protein-coupled receptor 154 with asthma and total IgE in a population of the Caribbean coast of Colombia.</a><br>Vergara C, Jiménez S, Acevedo N, Martínez B, Mercado D, Gusmão L, et al.<br>Clin Exp Allergy. 2009 Oct;39(10):1558-68. Epub 2009 Jul 16. |             |
|          | 2.                                                                                                                                           | <a href="#">Comprehensive testing of positionally cloned asthma genes in two populations.</a><br>Hersh CP, Raby BA, Soto-Quirós ME, Murphy AJ, Avila L, Lasky-Su J, et al.<br>Am J Respir Crit Care Med. 2007 Nov 1;176(9):849-57. Epub 2007 Aug 16.                                    |             |
|          | 3.                                                                                                                                           | <a href="#">G-Protein-coupled receptor polymorphisms are associated with asthma in a large German population.</a><br>Kormann MS, Carr D, Klopp N, Illig T, Leupold W, Fritzsche C, et al.<br>Am J Respir Crit Care Med. 2005 Jun 15;171(12):1358-62. Epub 2005 Mar 11.                  |             |
|          | 4.                                                                                                                                           | <a href="#">Characterization of a common susceptibility locus for asthma-related traits.</a>                                                                                                                                                                                            |             |

|                                                                                                                              |                                                                   |                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                              |                                                                   | Laitinen T, Polvi A, Rydman P, Vendelin J, Pulkkinen V, Salmikangas P, et al.<br>Science. 2004 Apr 9;304(5668):300-4.                                                                                                                                 |
|                                                                                                                              |                                                                   |                                                                                                                                                                                                                                                       |
| Gene:                                                                                                                        | <b>STAT6 (signal transducer and activator of transcription 6)</b> |                                                                                                                                                                                                                                                       |
|                                                                                                                              |                                                                   | Chr. <b>12q13</b>                                                                                                                                                                                                                                     |
| Studies:                                                                                                                     | 1.                                                                | <a href="#">Genetic haplotypes of Th-2 immune signalling link allergy to enhanced protection to parasitic worms.</a><br>Moller M, Gravenor MB, Roberts SE, Sun D, Gao P, Hopkin JM.<br>Hum Mol Genet. 2007 Aug 1;16(15):1828-36. Epub 2007 May 21.    |
|                                                                                                                              | 2.                                                                | <a href="#">A signal transducer and activator of transcription 6 haplotype influences the regulation of serum IgE levels.</a><br>Schedel M, Carr D, Klopp N, Woitsch B, Illig T, Stachel D, et al.<br>J Allergy Clin Immunol. 2004 Nov;114(5):1100-5. |
|                                                                                                                              | 3.                                                                | <a href="#">Association of a STAT 6 haplotype with elevated serum IgE levels in a population based cohort of white adults.</a><br>Weidinger S, Klopp N, Wagenpfeil S, Rummeler L, Schedel M, Kabesch M, et al.<br>J Med Genet. 2004 Sep;41(9):658-63. |
| *Reviews, meta-analyses of already published data, and GWAS-based studies were not taken into account in the present search. |                                                                   |                                                                                                                                                                                                                                                       |