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Review

Understanding the genetic regulation of IgE production

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ABSTRACT

Immunoglobulin E (IgE) is a key mediator of anti-parasitic and anti-tumour immunity. However it is also a critical component of atopic and autoimmune diseases, and elevated serum IgE levels are a common indicator of immune dysregulation. In this review we survey the literature on genetic associations of elevated IgE in humans and mice. We find that defects in a limited number of pathways explain the majority of gene associations with IgE. Commonly, elevated IgE is associated with defects in Th bias and B cell class switching, severe T cell tolerance defects and defects in immunity at the host–environment interface. These genetic data demonstrate the mechanisms of control over IgE production and the manner in which they can be circumvented.

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1. Introduction

IgE is commonly thought of as a parasite-specific immunological defence. However there is growing evidence that the traditional role for IgE underestimates its importance in immune function. In a healthy response, IgE serves as an important initiator of humoral memory responses and may also mediate anti-tumor immunity^{1,2}. Despite the beneficial role of IgE, serum IgE concentrations in a healthy individual are typically very low, on the order of ~150 ng/ml (compared with 10 mg/ml for IgG). This is due, in part, to a combination of molecular properties that ensure tighter control over IgE than other antibody isotypes. IgE production is limited by alternative polyadenylation³, skewing production 100-fold towards secretion rather than the membrane-bound form. Furthermore the cytoplasmic domain of membrane-bound IgE has a reduced efficiency of signalling (10-fold less efficient than the IgG1 cytoplasmic domain)⁴. Together these reduce the memory and activation response of IgE-producing B cells, resulting in limited production. Serum levels are further reduced by the very short half-life of free (unbound) IgE, of only 5–8 h compared to ~10 days for IgG1⁵.

The necessity for the unusually tight control that is kept over IgE becomes apparent when the disease associations with IgE are considered. Most commonly, serum IgE levels have a strong correlation with susceptibility to, and severity of, the atopic diseases of allergic asthma, rhinitis, conjunctivitis, atopic eczema, food allergy and oral allergy syndrome. In these diseases, serum IgE levels may be more than 10 times the normal level. Allergen-specific IgE antibody

concentrations may be over 1000 times higher than the minimum level of detection (~0.6 ng/ml) found in the majority of healthy individuals⁶. Beyond the atopic diseases, there is also evidence for IgE as a pathological mediator in autoimmune diseases, such as multiple sclerosis⁷, inflammatory bowel disease^{8,9}, rheumatoid arthritis¹⁰ and bullous pemphigoid^{11,12}. A number of severe monogenic disorders also exist which have serum IgE concentrations far in excess of the elevations in atopy.

Understanding the genetic control over IgE production provides a way to probe the functional genetics of the disorders which include excessive IgE production. Available genetic data indicates that IgE is a distinct subphenotype of atopic diseases with discrete genetic control independent of other subphenotypes involved in disease formation¹³. Furthermore, control of serum IgE concentration is likely to be more amenable to genetic dissection than the complex atopic disease phenotypes, as the former has a lower degree of environment input – the genetic component of the variation observed in serum IgE within human populations is estimated at 40–80% for total IgE and 30–40% for specific IgE^{13–18}. This review attempts to relate known genes to potential mechanisms of IgE hyperproduction by using the functional data that has risen from recent studies in humans and mice.

2. Genetic linkage with increased serum IgE

There are several sources of genetic information on serum IgE concentration. The first are the monogenic disorders including an IgE component, such as Hyper IgE syndrome (HIES). The second are the complex genetic diseases which include IgE production, such as allergic asthma and rhinitis. The third source of genetic information on serum IgE concentration is that of mouse models with heightened

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IgE levels (Supplementary Table 1), which adds valuable mechanistic data.

Of the monogenic human disorders associated with elevated IgE (Table 1), the one best characterised by increased IgE production is HIES, where extreme IgE production is the key clinical feature. HIES exists as in clinically distinct sporadic, dominant familial and recessive familial forms. Dominant negative mutations in *STAT3* (signal transducer and activator of transcription 3) have been found as *de novo* mutations in both sporadic cases^{19,20} and dominant familial cases²⁰. Other mapping studies have found linkage to chromosomal regions with no obvious candidates²¹. The recessive form of the disease has been linked to mutations in *DOCK8*²² and *TYK2*²³.

A cluster of monogenic disorders that include excessive IgE production are the partial T cell immunodeficiencies. These include ADA deficiency (caused by mutations in *ADA*), Omenn syndrome (caused by mutations in *DCLRE1C*, *IL2RG*, *IL7RA*, *RAG1*, *RAG2* or *RMRP*), Wiskott–Aldrich syndrome (caused by mutations in *WAS*), *ZAP70* deficiency (caused by mutations in *ZAP70*) and 22q11 syndrome (caused by deletion of 22q11). Two other diseases, Autoimmune Lymphoproliferative Syndrome II (ALPSII, caused by mutations in *CASP10*) and Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX, caused by mutations in *FOXP3*) are characterised by general failure of self-tolerance and can include elevated levels of IgE^{24,25}. Finally, two diseases best characterised as primary skin disorders are commonly associated with increased IgE production – Netherton Syndrome (caused by mutations in *SPINK5*) and Ichthyosis vulgaris (caused by mutations in *FLG*).

In addition to the severe monogenic disorders described above, increased serum IgE levels are associated with the less severe and more common atopic diseases, allergic asthma, rhinitis, conjunctivitis, atopic eczema, food allergy and oral allergic syndrome. These diseases have a more complex genetic basis than the monogenic disorders, with multiple genes influencing different facets of the genetic susceptibility to disease. However, despite the wealth of genetic data on these diseases, relatively few studies have looked at genetic control over the IgE component specifically, and therefore for most gene linkages it is unknown whether they are linked to the IgE component or a non-IgE disease component. For example, *FOXJ1* is linked with allergic rhinitis, and is thus associated with increased IgE levels, however a mapping study of serum IgE within allergic rhinitis patients showed no link of *FOXJ1* with serum IgE concentrations, indicating that *FOXJ1* polymorphisms contribute to allergic rhinitis by

modulating a non-IgE component of susceptibility²⁶. Despite this proviso, a number of studies have looked at the linkage of polymorphisms to serum IgE as a surrogate for atopic disease, either in the healthy population or among atopic patients (Table 2). These studies have demonstrated that polymorphisms in *CD14*^{27,28}, *CD40*²⁹, Eotaxin family members^{30,31}, *FCER1B*³², *HLA-DRB1*^{33,34}, *ICOS*³⁵, *IFNGR*³⁶, *IL13*³⁷, *IL21R*³⁸, *IL4*³⁹, *IL4R*⁴⁰, *NOD1*⁴¹, *PAFAH* (Platelet Activating Factor acetylhydrolase)⁴², *PHF11*⁴³, *SPP1*⁴⁴, *STAT6*^{45,46} and *TNF*⁴⁷ are linked to total IgE levels. As would be expected, most of these genes have also shown linkage to certain clinical features of atopic diseases. As most of these associations have been determined by hypothesis-driven testing rather than genome-wide association, this list should not be considered conclusive or even necessarily reflective of the most important genetic contributors, but it does indicate a role for these genes in control over serum IgE levels. The first genome-wide scan for serum IgE identified *FCER1A*, *STAT6* and *RAD50* as linked genes within the German population⁴⁸.

3. Mechanisms underlying increased IgE production

3.1. Regulation of class switching to IgE and the Th bias

B cell class switching to IgE is a tightly controlled process regulated by interaction with CD4 T cells and the cytokine microenvironment (Fig. 1). It comes as no surprise, therefore, that many of the genes that regulate serum IgE levels have a distinct role in signalling the B cell response to these stimuli. It is well established that IL-4 and IL-13, cytokines produced by Th2 cells and B cells, promote isotype class switching to IgE in B cells^{49,50}. These cytokines are present at increased levels in atopic patients⁵¹, so it is expected that the

Table 2

| Genes associated with elevated IgE serum concentrations in atopic patients and the healthy population.

Gene	Selected associations	Refs	OMIM
<i>CCL11</i> (<i>EOTAXIN1</i>)	Linkage to serum IgE, asthma	30,124	601156
<i>CCL26</i> (<i>EOTAXIN3</i>)	Linkage to serum IgE, eosinophilic esophagitis	31,125	604697
<i>CD14</i>	Linkage to serum IgE, myocardial infarction	27,28,126	158120
<i>CD40</i>	Linkage to serum IgE, immunodeficiency with hyper IgM	29,127	109535
<i>FCER1A</i>	Linkage to serum IgE in atopy. Linkage to serum IgE in genome-wide scan.	48,128	147140
<i>MS4A2</i> (<i>FCER1B</i>)	Linkage to serum IgE, asthma, atopy, dermatitis.	32	147138
<i>IFNGR</i>	Linkage to serum IgE, atypical mycobacterial infection	36,129	107470
<i>HLA-DRB1</i>	Linkage to serum IgE, specific IgE, sarcoidosis	33,34,130	142857
<i>ICOS</i>	Linkage to serum IgE	35	604558
<i>IL13</i>	Linkage to serum IgE, asthma and atopy	37 131	147683
<i>IL21R</i>	Linkage to serum IgE	38	605383
<i>IL4</i>	Linkage to serum IgE	39	147780
<i>IL4R</i>	Linkage to serum IgE, atopy, asthma	40,132	147781
<i>NOD1</i>	Linkage to serum IgE, inflammatory bowel disease	41,133	605980
<i>PAFAH</i>	Linkage to serum IgE in atopic disease, asthma	42	601690
<i>PHF11</i>	Linkage to serum IgE in asthma	43	607796
<i>SPP1</i>	Linkage to serum IgE	44	166490
<i>STAT6</i>	Linkage to serum IgE, asthma. Linkage to serum IgE in genome-wide scan.	45,46,48	601512
<i>RAD50</i>	Linkage to serum IgE in genome-wide scan.	48	604040
<i>TNF</i>	Linkage to serum IgE, asthma, susceptibility to mucocutaneous leishmaniasis, rheumatoid arthritis, inflammatory bowel disease	47,134–136	191160

Table 1

| Monogenic disorders resulting in elevated IgE serum concentrations.

Disease	Gene	Refs	OMIM
ADA deficiency	<i>ADA</i>	104–106	102700
Autoimmune Lymphoproliferative Syndrome II (ALPSII)	<i>CASP10</i>	24	601762
Omenn syndrome (*including related cases)	<i>DCLRE1C</i> * <i>IL2RG</i> <i>IL7RA</i> <i>RAG1</i> <i>RAG2</i> <i>RMRP</i>	107–111	603554
Hyper-IgE syndrome (autosomal dominant and sporadic forms)	<i>STAT3</i>	19,20	147060
Hyper-IgE syndrome (autosomal recessive form)	<i>TYK</i> <i>DOCK8</i>	22,112	243700
Ichthyosis vulgaris	<i>FLG</i>	113,114	146700
Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX)	<i>FOXP3</i>	25	304790
Netherton disease	<i>SPINK5</i>	115	256500
Wiskott–Aldrich syndrome	<i>WAS</i>	116–119	301000
<i>ZAP70</i> deficiency	<i>ZAP70</i>	120	176947
22q11 syndrome (DiGeorge syndrome/Velocardiofacial syndrome)	~90% due to deletion of 22q11	121–123	188400/ 192430

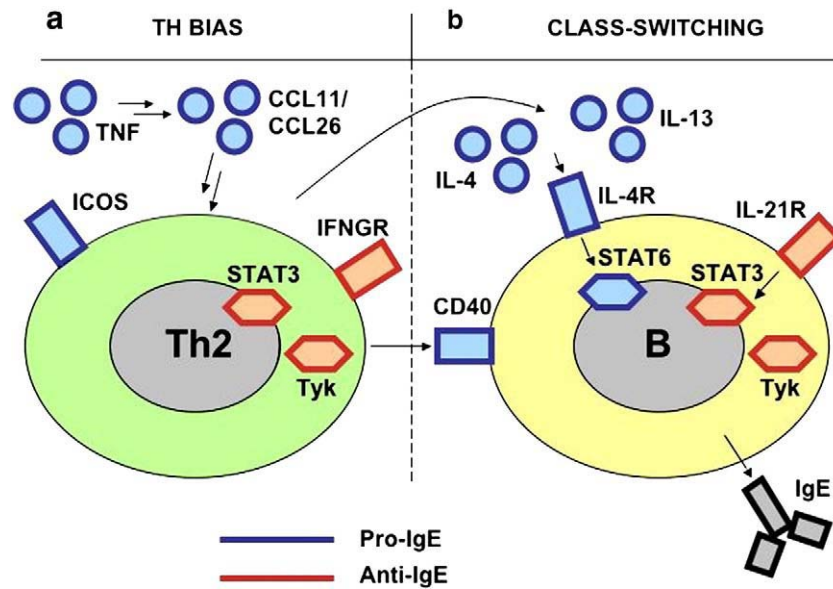


Fig. 1. Mechanisms of elevated IgE levels through mutations in human genes. Regulators of serum IgE with a role in Th bias or B cell class switching. (a) IgE-linked genes whose protein products have a role in skewing the Th bias include *CCL11*, *CCL26*, *ICOS*, *TNF*, *IFNGR*, *STAT3* and *TYK2*. Among these, *CCL11*, *CCL26*, *ICOS* and *TNF* are known to promote a Th2 bias, such that their IgE-associated alleles likely confer increased expression or function. In contrast, *IFNGR*, *STAT3* and *TYK2* may normally function to antagonise Th2 polarisation, since loss-of-function alleles of these genes result in elevated IgE. (b) IgE-linked genes whose protein products have a role in regulating B cell class switch recombination to IgE include *IL4*, *IL13*, *IL4R*, *STAT6*, *CD40*, *IL21R*, *STAT3* and *TYK2*. Among these, *IL4*, *IL13*, *IL4R*, *STAT6* and *CD40* are known to positively regulate switching to IgE, indicating that alleles associated with elevated IgE are hypermorphic. In contrast, loss-of-function alleles of *IL21R*, *STAT3* and *TYK2* cause elevated IgE, consistent with a role for their protein products in negatively regulating IgE class switching.

association of both *IL4* and *IL13* alleles with increased serum IgE^{37,39} represents the effect of hypermorphic alleles increasing class switching of B cells to IgE. Likewise, the association of *IL4R* and *STAT6* alleles with serum IgE levels^{40,45,46} likely reflects enhanced signalling through the shared IL-4/IL-13 receptor and the signalling mediator STAT6. In the case of *IL4R*, this hypothesis has been confirmed, as the polymorphism with enhanced signalling capacity was the one associated with higher IgE levels⁴⁰. Alongside these soluble factors, the engagement of CD40 on B cells by CD40L provides a second signal for IgE class switching⁵², and a *CD40* polymorphism resulting in increased expression has been associated with elevated IgE²⁹.

In contrast to positive regulators of class switch recombination, the cytokines IL-10 and IL-21 act directly upon activated B cells to reduce the efficiency of class switching towards IgE^{53,54}. In this case, the linkage of *IL21R*³⁸, encoding the receptor for IL-21, and *STAT3*^{19,20} and *TYK2*²³, encoding signalling mediators for IL-10 and IL-21^{55,56}, may represent hypomorphic alleles reducing the influence of IL-10 and IL-21, and hence promoting IgE class switching. Functional allelic studies on the HIES-associated alleles of *STAT3* and *TYK2* demonstrate that the alleles are dominant negative and loss-of-function, respectively^{19,20,23}. While functional allelic studies have not been performed on the IgE-linked allele of *IL21*, *IL21*^{-/-} mice have increased serum IgE levels⁵⁴. Of interest, the *IL21*^{-/-} mice show lower IgG1 production and impaired Th1 responses to *Toxoplasma gondii*, demonstrating that IL-21 does not cause a global defect in class switching, and indeed cooperates with IL-4 in IgG1 class switching⁵⁴. This assumption is complicated, however, by conflicting results on human IL-21, which suggest it may have an opposite function to murine IL-21 under certain conditions⁵⁷. If this proves to be the case, the human *IL21R* allele may be a hypermorph rather than a hypomorph, and the association of hypomorphic *STAT3* and *TYK2* alleles with elevated IgE may be despite of, rather than due to, their role in IL-21 signalling (see below).

Other gene associations are likely to increase serum IgE levels by altering the Th bias towards a Th2 phenotype, and thereby indirectly promoting the cytokine milieu capable of enhancing IgE

class switching. Genes operating through this mechanism likely include *IFNGR*³⁶, the eotaxin family members^{30,31} and *TNF*⁴⁷. *TNF* has been demonstrated to cause an increase in eotaxin production⁵⁸, which causes the recruitment of CCR3-expressing eosinophils, mast cells and Th2 cells. Hyperactivity of either the *TNF* or *EOTAXIN* loci may thereby enhance IgE levels by creating a microenvironment rich in the Th2 cytokines IL-4 and IL-13, stimulating IgE class switching. This model is supported by studies showing that inhibition of CCR3 in mice reduces atopic disease⁵⁹. *IFNGR*, by contrast, is likely to be enhancing IgE levels by reducing Th1 numbers³⁶. As the receptor for IFN γ , IFN γ R skews T cell differentiation towards the Th1 pathway, thus enhancing the expression of cytokines antagonistic towards IgE class switching and production^{60–62}. This indicates that the *IFNGR* alleles associated with increased IgE production are likely to be hypomorphic.

It is likely that *STAT3* and *TYK* contribute to elevated IgE production by creating a Th bias, in addition to their disputed role in class switching. Patients with HIES have been shown to have an imbalance in the Th1/Th2 ratio upon *in vitro* stimulation^{63,23}. In addition to being important for IL-10 and IL-21 signalling, *STAT3* and *TYK* also have a role in IL-6 and IL-23 signalling. As key mediators of Th17 differentiation⁶⁴, this loss reduces the capacity to differentiate into Th17 cells⁶⁵. This defect enhances the commitment to alternative T cell lineages, including the Th2 lineage^{23,66}.

Polymorphisms in the genes encoding the high affinity IgE receptor, both the alpha and beta chains, have been linked to IgE^{32,48}. One possibility is that these polymorphisms increase receptor expression or activity and thereby heighten the response of mast cells and basophils to antigen engagement by surface bound IgE. As this response includes the synthesis of IL-4, these alleles would fall under the category of Th2 promoting. This is supported by the observation of increased Fc ϵ R1 expression in subjects with *FCER1* polymorphisms. However this should be interpreted carefully, as increased serum IgE in turn upmodulates Fc ϵ R1 expression, making it difficult to determine whether increased Fc ϵ R1 expression is a cause or effect of elevated IgE.

3.2. Defects in general tolerance mechanisms

The Th2 response can be accentuated by Th bias deviation away from non-Th2 (Th1, Th17) responses. However the Th2 response can also be increased concurrently with Th1 and Th17 responses in cases of cataclysmic tolerance failure. The IgE production in IPEX is an example of this latter pathway. Studies in mouse models have shown that Foxp3 is essential for the differentiation of Foxp3⁺ regulatory T cells^{67–69}. In the absence of Foxp3⁺ regulatory T cells, the restraint on all lineages of effector T cells is removed, with amplification of the Th1, Th2 and Th17 responses⁷⁰. The excessive IgE production in mouse strains with defects in other fundamental tolerance pathways acting independent of regulatory T cells, such as TGFβ⁷¹, indicates that this response is not specific to loss of Foxp3⁺ regulatory T cells.

In this case, mutations in *CASP10*, *ICOS* and *PAFAH* may induce excessive IgE production by similar non-specific tolerance failures. The mutations of *CASP10* associated with ALPSII reduce the functionality of Caspase 10 and hence reduce transmission of the Fas-dependent apoptotic signal, critical for peripheral tolerance²⁴. Likewise, the mutations of *PAFAH* associated with excessive IgE production result in reduced affinity of PAFAH for its substrate, Platelet-activating factor (PAF)⁴². The resulting increase in serum PAF levels is capable of providing pro-inflammatory and anti-apoptotic signalling to platelets, neutrophils, macrophages and B cells^{72,73}. In the case of *ICOS*, the essential role of ICOS-ICOSL interactions in driving the proliferation of activated T cells indicates that hypermorphic alleles in humans may represent a non-specific tolerance defect. In mice, knockouts of *Icos* have reduced T cell activation, resulting in reduced IL-4 production and IgE^{74–76}, while defects in the *Icos*-inhibitor Roquin result in spontaneous T cell activation and elevated IgE production⁷⁷.

Another way in which a general defect in immune tolerance can occur is through partial T cell immunodeficiency⁷⁸. A multitude of genes are linked to both partial T cell immunodeficiency and elevated IgE production in both humans (*ADA*, *DCLRE1C*, *IL2RG*, *IL7RA*, *RAG1*, *RAG2*, *RMRP*, *WAS*, *ZAP70*) and mice (*Lat*, *Lcp2*, *Cbl*, *Rag2*, *Tcra*, *Wip*, *Zap70*). Despite the expectation that reduced T cell number and function would result in reduced immune activity, the frequency of this dual presentation indicates a causal linkage. Numerous experiments in mouse models indicate that T cell immune tolerance mechanisms breakdown in situations of partial immunodeficiency⁷⁸. A reduction in the number of T cells being produced in the thymus is likely to reduce the efficiency of thymic negative selection due to the reduction in lymphotoxin production creating a disordered thymic microenvironment^{79–81}. In addition, the restriction of thymic production to an oligoclonal repertoire will reduce the spectrum of FOXP3⁺ regulatory T cells, and mouse transfer experiments have shown that an expanded oligoclonal repertoire of Foxp3⁺ regulatory T cells is unable to control the effector T cell response, leading to enhanced serum IgE levels^{82,83}. A third mechanism by which partial T cell immunodeficiency may result in immune tolerance breakdown is through a reduction in the peripheral numbers of T cells, and hence increased bioavailability of IL-7^{84,85} and CD80/CD86⁸⁶, leading to increased activation of effector T cells and reduced efficiency of peripheral deletion^{84,85,87}.

For defects in the gene *WAS*, in *Was*^{−/−} mice and Wiskott–Aldrich syndrome patients, the immune tolerance defects resulting in elevated production of IgE may be two-fold. Firstly, the mutations result in partial T cell immunodeficiency, which will cause tolerance breakdown as above. Secondly, *WAS* appears to be required for the proper production⁸⁸, homeostasis⁸⁹ and function^{88,90,91} of FOXP3⁺ regulatory T-cells.

3.3. Defects in immunity and barrier mechanisms

It is striking that several of the monogenic conditions associated with increased IgE are primarily skin defects. Both Netherton disease

(caused by *SPINK5* mutations) and Ichthyosis vulgaris (caused by *FLG* mutations) include severe defects to keratinocyte function and the skin barrier, resulting in an increase in infectious disease. Even among atopic dermatitis patients, while the majority of patients begin with elevated IgE, a minority of patients develop atopic dermatitis with normal IgE levels but experience elevated IgE after prolonged disease⁹². The same phenomenon is observed in multiple IgE-prone mouse strains, with *Flg*^{5303ΔA} mice, *Ttc7^{sn}* mice, NC/Nga mice and NOA mice all having primary defects in the skin layer and elevated IgE^{93–96}. This correlation suggests that there is something peculiarly Th2-promoting about the skin microenvironment of these patients and mice. More specifically, it is likely that the production of elevated IgE directly relates to chronic stimulation of the immune system through persistent infection at the compromised barrier, as NC/Nga mice kept in an SPF environment to prevent infection of the defective skin do not progress to elevated IgE serum concentrations⁹³ and percutaneous administration of antigen in *Flg*^{5303ΔA} mice is sufficient to provoke antigen-specific IgE responses⁹⁶.

In light of the importance of Th17 cells in combating cutaneous infections⁹⁷, it is feasible that part clinical phenotype of HIES is due to the defect in Th17 differentiation due to *STAT3* and *TYK* deficiency, leading to increased rates of staphylococcal and candida infections^{23,65}. Keratinocytes and bronchial epithelial cells have a stronger dependence on Th17-dependent cytokines to provoke anti-microbial responses than other cell types⁹⁸. Th17-specific defects in the immune system may therefore act analogously to breaches in the barrier mechanism, weakening innate defences. Likewise, a portion of the elevated IgE production in IPEX patients may be due to the autoimmune mediated destruction of the skin barrier, leading to excessive cutaneous infection. The association of both *NOD1* and *CD14* with elevated IgE^{27,28,41} may also represent primary immune defects driving excessive IgE production through altered susceptibility to infection, as the protein products of both genes recognise microbial productions (diaminopimelic acid and LPS, respectively). The relationship is complicated, however, as the genotypic effect of each allele depends upon exposure to infections^{99–101}.

3.4. The curious case of MHC presentation

An association which does not fit easily into any of the three main categories outlined above is that of *HLA-DRB1*. There is little theoretical basis upon which to assume that HLA alleles could non-specifically promote IgE production, and the association of elevated IgE with the MHC locus in both humans^{33,34} and the Brown–Norway rat¹⁰² make it unlikely that a unique aspect of *HLA-DRB1* alleles non-specifically promotes IgE production. The most likely hypothesis is that certain *HLA-DRB1* alleles are highly adapt at presenting antigen which is intrinsically IgE-promoting, for example the association of *DRB1*13* with enhanced IgE production against *Schistosoma mansoni* antigens¹⁰³. This hypothesis would also explain the greater degree of variation in total IgE concentration caused by *HLA-DRB1* in Australian Aborigines of the Kimberly region (33%), with endemic hookworm infection, than Australian Caucasians (4%)^{33,34}. However, *HLA-DRB1* is responsible for a greater proportion of the variation in total serum IgE than in IgE with recognised specificity in both populations (33% vs 17% in Australian Aborigines, 4% vs 2–3% in Australian Caucasians^{33,34}). Therefore, if *HLA-DRB1* alleles are promoting IgE production through enhanced responses to specific antigens, the inciting antigens remain unknown.

4. Concluding comments

Despite the paucity of genome-wide studies performed on serum IgE concentration, there is a rich trove of genetic information on control of IgE production thanks to association studies within atopic diseases and the spectrum of monogenic disorders including elevated IgE production. Of the more than 30 human gene associations outlined

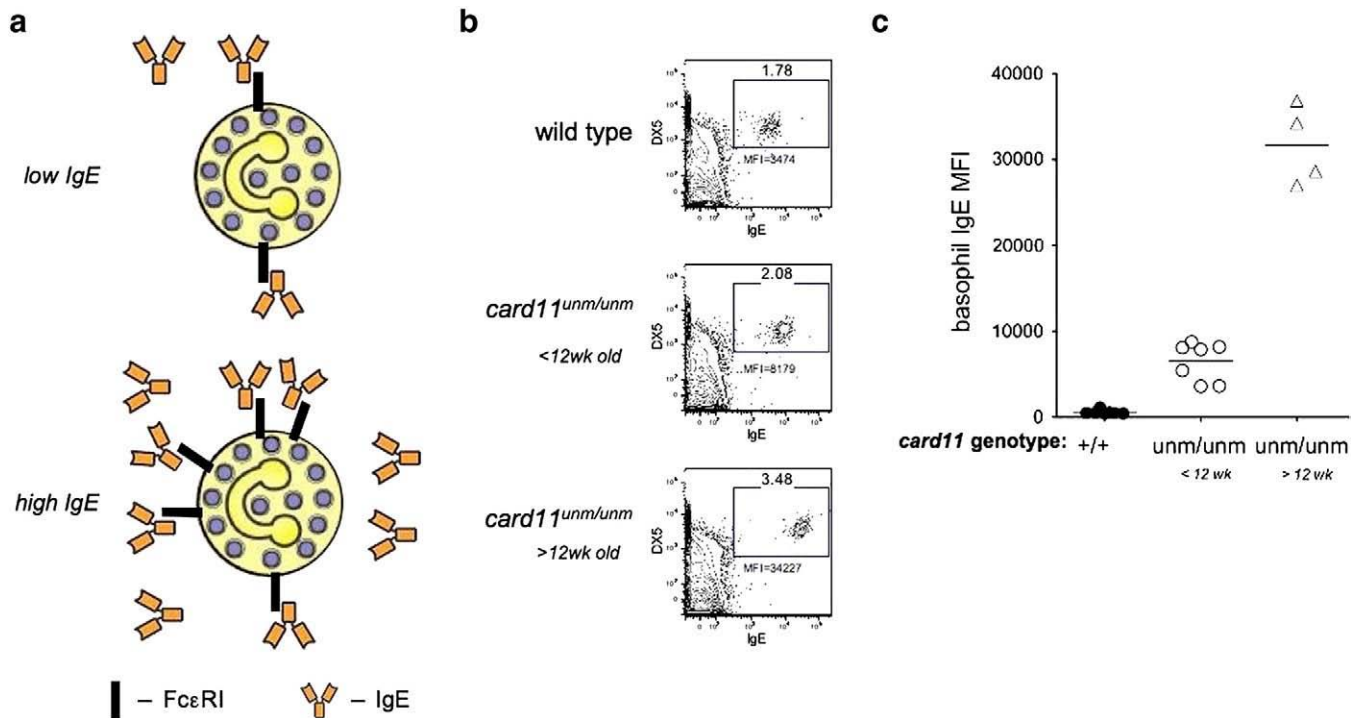


Fig. 2. A strategy for mass screening of serum IgE variation. (a) Flow cytometric detection of IgE concentrations can be performed through the measurement of serum IgE captured by basophils. (b) Basophils in an elevated IgE environment, such as *card11*^{unm/unm} mice, soak up extra IgE, which is detectable via a shift in anti-IgE staining. (c) Changes in IgE MFI robustly report minor shifts in IgE concentration, such as the early elevation in *card11*^{unm/unm} mice, prior to the advent of atopic disease. The full protocol of this assay will be detailed in a manuscript in preparation.

in this review, around half have known functions in Th bias and B cell IgE class switch recombination that explain their association with elevated IgE production. Strikingly, however, half of the known gene associations are apparently unrelated to Th bias or class switching, and instead reflect generalised defects in immune tolerance or host–environment interface immunity. Notably, these latter associations have generally been found by serendipity while the Th bias and class switching associations were generally found by a candidate approach. This makes it highly likely that further studies will find more gene associations that cause elevated IgE production through less-well characterised pathways. A necessary component for unbiased screening for genes involved in this process is a simple and sensitive assay to test for variations in IgE production. In order to screen a genome-wide ENU mutagenesis mouse library, we have developed a simple, basophil-based flow cytometry-based assay that is very sensitive to small changes in IgE production preceding hyper-IgE and atopic disease (Fig. 2). It is expected that use of such an assay in a systematic manner will not only detect mutations in the Th2–IL4–IgE pathway, but also in a diverse array of immunity and tolerance mechanisms that feed into IgE production in unexpected manners. In support of this hypothesis, the genes most strikingly associated with elevated IgE, such as *STAT3* and *TYK2* in HIES, have a function in both Th bias/class switching and an additional mechanism, in these cases Th17 production (host–environment interface immunity). IgE-associated genes may therefore represent a rich resource for finding novel tolerance and interface immunity mechanisms.

Conflict of interest statement

None to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.blre.2010.06.002.

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Supplementary Table 1 | Knockout and mutant mouse strains exhibiting elevated serum IgE concentrations

Variant	MGI	References
<i>Bcl6</i> ^{-/-}	2158439	¹
<i>Card11</i> ^{unm}	3045963	²
<i>Ctse</i> ^{-/-}	107361	³
<i>Dock2</i> ^{-/-}	2149010	⁴
<i>H1r</i> ^{-/-}	107619	⁵
<i>Il21r</i> ^{-/-}	2446509	⁶
<i>Id2</i> ^{-/-}	2384134	⁷
<i>Itch</i> ^{a18H}	1856404	⁸
<i>Fcer2a</i> ^{-/-}	95497	⁹
<i>Flg</i> ^{5303delA}	95553	¹⁰
<i>Foxp3</i> ^{-/-}	2654936	¹¹
<i>Foxp3</i> ^{sf}	1857034	^{12,13}
<i>Hnrnpd</i> ^{-/-}	3693617	¹⁴
<i>Lat</i> ^{Y136F}	2182312;2388631	^{15,16}
<i>Lat</i> ^{Y778/9F}	3510778	¹⁷
<i>Lcp2</i> ^{-/-} <i>Cbl</i> ^{-/-}	2180002;2180576	¹⁸
<i>Lcp2</i> ^{twp}	3614800	C. Goodnow, personal communication
<i>Nfatp</i> ^{-/-} <i>Nfatc3</i> ^{-/-}	2182740; 2182778	¹⁹
<i>Nfatp</i> ^{-/-}	2182740	^{20,21}
<i>Relb</i> ^{-/-}	103289	²²
<i>Rag2</i> ^{R229Q}	3713766	²³
<i>Rc3h1</i> ^{roq}	2685397	²⁴
<i>Runx3</i> ^{-/-}	3641439	²⁵
<i>Tcra</i> ^{-/-}	2180883	²⁶
<i>Tgfb1</i> ^{-/-}	1857671	²⁷
<i>Ttc7</i> ^{sn}	1856879	²⁸
<i>Wip</i> ^{-/-}	2178802	²⁹
<i>Zap70</i> ^{mrd/mrt}	3614796;3614790	³⁰

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