

Genetic regulation of immunoglobulin E level in different pathological states: integration of mouse and human genetics

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ABSTRACT

Immunoglobulin E (IgE) first evolved in mammals. It plays an important role in defence against helminths and parasitic infection and in pathological states including allergic reactions, anti-tumour defence and autoimmune diseases. Elucidation of genetic control of IgE level could help us to understand regulation of the humoral immune response in health and disease, the etiology and pathogenesis of many human diseases, and to facilitate discovery of more effective methods for their prevention and cure. Herein we summarise progress in the genetics of regulation of IgE level in human diseases and show that integration of different approaches and use of animal models have synergistic effects in gaining new knowledge about both protective and pathological roles of this important antibody.

Key words: immunoglobulin E, genetic influence, serum level, multiple interacting genes, mutation in a single gene, hypothesis-driven approach, hypothesis-independent manner, complex diseases, human, mouse.

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I. INTRODUCTION

Mammals express five classes of antibodies: IgM, IgD, IgG, IgA, and IgE, of which only IgM, IgD, and IgA are present in non-mammalian tetrapods (amphibians, reptiles and birds). Mammalian IgE and IgG have evolved through gene duplication and subsequent evolution of IgY, an ancient Ig class found in amphibians, reptiles and birds. In this duplication and evolution the anaphylactic and opsonic activities of IgY were separated between IgE and IgG, respectively. Anaphylactic reaction has life-threatening side effects and its separation to a distinct molecule allowed its specific downregulation without affecting opsonic capacity (Warr, Magor & Higgins, 1995). This review will concentrate on the genetic control of IgE level in the human and mouse, because these two species are the most extensively analysed. We show a synergistic effect of integration of human and mouse studies that opens novel research perspectives and strategies.

II. THE MOLECULAR REGULATION OF IgE PRODUCTION

IgE is predominantly present in lung, skin, and mucous membranes. It plays a crucial role in defence against helminths and other parasitic infections, in development of allergic reactions, in some anti-tumour defences and in several autoimmune diseases. Due to its involvement in many pathological conditions, analysis of factors that regulate IgE production is very important for understanding the etiology and pathogenesis of human diseases and for the discovery of more effective methods for their cure.

In healthy individuals, the level of IgE is tightly regulated, with very low serum concentration in comparison to other classes of antibodies. This regulation involves a complex network of interactions. The production of IgE is initiated as a cascade.

B lymphocytes derive from haematopoietic stem cells by a set of differentiation events. This process occurs in the foetal liver and, in adult life, in the bone marrow (Achatz-Straussberger *et al.*, 2009). Immunoglobulin variable region exons are assembled from component V, D, and J gene segments *via* V(D)J recombination. V(D)J recombination is initiated in developing lymphocytes by the recombination-activating gene (RAG) endonuclease, which consists of the RAG1 and RAG2 proteins (Matthews & Oettinger, 2009).

Upon activation by antigen in peripheral lymphoid organs, mature B cells may undergo IgH class-switch recombination (CSR), a process in which the IgH μ constant region exons ($C\mu$) are deleted and replaced by one of several sets of downstream C_H exons (e.g. $C\gamma$, $C\epsilon$, and $C\alpha$), termed C_H genes. CSR is initiated by activation-induced (cytidine) deaminase (AID), which is also essential for the introduction of somatic hypermutations in the variable regions of the Ig (Muramatsu *et al.*, 2000).

IgE switching largely occurs through a sequential CSR mechanism, in which activated B cells first switch from IgM to IgG1 (in mouse) or to IgG4 (in human) *via* CSR from $C\mu$ to $C\gamma 1$, followed by switching to IgE *via* a 'second step' CSR from $C\gamma 1$ to $C\epsilon$, but a route *via* a direct switch from $C\mu$ to $C\epsilon$ has been also described (see below).

The ratio of IgE and IgG1 antibodies is influenced by the dose and frequency of immunisation (Vaz, Vaz & Levine, 1971), production of cytokines by follicular helper T cells (TFh) (Liang *et al.*, 2012), the nature of the antigen-presenting cells (APCs) (De Becker *et al.*, 1994) and maturity of the responding B cells (Wesemann *et al.*, 2011). Interleukin 4 (IL-4) is required for IgE production as *IL4^{KN2/KN2}* mice [created by replacing the first two exons of IL-4 with a human cluster of differentiation 2 (CD2)-encoding sequence] are unable to mount an IgE response (Liang *et al.*, 2012). IL-21R deficiency leads to a state of pan-hypogammaglobulinaemia while promoting high titres of IgE (Ozaki *et al.*, 2002) due to the role of IL-21 in the persistence of germinal centres (GCs) (Zotos *et al.*, 2010)—structures that are not favourable for IgE⁺ cells (Xiong *et al.*, 2012) (see below). Although polymorphisms in *IL13* influence IgE level (Graves *et al.*, 2000; Liu *et al.*, 2004; Donfack *et al.*, 2005; Maier *et al.*, 2006; Beghe *et al.*, 2010) (see Section IV.1a), IL-13 is not necessary for high-affinity B cell responses (Liang *et al.*, 2012).

It has recently been shown that mouse immature B cells from bone marrow and spleen switch to IgE in a direct $C\mu \rightarrow C\epsilon$ CSR, whereas the mature B cells have a propensity to switch *via* an IgG1 intermediate (Wesemann *et al.*, 2011). The type of switching influences affinity of the generated antibodies. High-affinity IgE is generated through sequential CSR ($C\mu \rightarrow C\gamma 1 \rightarrow C\epsilon$) in which an intermediary IgG phase is necessary for the affinity maturation of the IgE response, because the IgE inherits somatic hypermutations and high affinity from the IgG phase (Xiong *et al.*, 2012). This development of somatically hypermutated and affinity-matured IgG1⁺ B cell intermediates takes place within GCs (Erazo *et al.*, 2007). By contrast, low-affinity IgE is generated through direct CSR ($C\mu \rightarrow C\epsilon$) and is much less mutated (Xiong *et al.*, 2012) and also can occur outside GCs.

IgE⁺ B cells are exceptional because they are largely found outside GCs (Xiong *et al.*, 2012). *Bcl6*-deficient mice have severely impaired GCs formation and no affinity maturation, but they harbour an increased number of IgE⁺ cells (Ye *et al.*, 1997). Similarly, deficiency of dedicator of cytokinesis 8 (*Dock8*) caused unstable GCs in mice (Randall *et al.*, 2009) and hyper IgE syndrome in humans (Engelhardt *et al.*, 2009; Zhang *et al.*, 2009). In addition, Aalberse & Platts-Mills (2004) compared the relative dynamics of development of allergy and synthesis of IgE and pointed out that different strength of T helper 2 cell (Th2) response influences the generation of GCs. Hence, the B cells in GCs and outside GCs differ in the resulting antibody response as well as in generation of plasma and memory cells.

All antigen-activated B cells express low-affinity Fc receptor for IgE, Fc ϵ RII (CD23), which enables B cells to present antigens to the cognate Th cells regardless of the

specificity of the B cell's own antigen receptor. This process is known as 'facilitated antigen presentation' and may lead to 'epitope spreading' to unrelated antigens. Finally, the secretion of IgE is controlled by several feedback mechanisms that engage high-affinity Fc receptor for IgE (Fc ϵ RI) on mast cells and IgE-sensitized APCs and Fc ϵ R2 on B cells. Fc ϵ RI provides a positive feedback. Soluble Fc ϵ R2 with its co-receptor CR2 (CD21) appears to enhance IgE production at low IgE concentrations (only in humans), whereas Fc ϵ R2 on B cells suppresses IgE production at high IgE concentrations (Gould & Sutton, 2008; Burton & Oettgen, 2011; Galli & Tsai, 2012).

Many other genes that are involved in regulation of IgE production are described in Section IV.

III. THE ROLE OF IgE IN DIFFERENT PATHOLOGICAL STATES

Selective IgE deficiency is currently defined as a significant decrease in the levels of IgE in a patient whose other immunoglobulin levels, including IgG subclasses and IgA levels are normal. It is usually asymptomatic, but may be associated with recurrent respiratory infections, chronic fatigue, and autoimmune disorders (Smith *et al.*, 1997). The pathogenesis of selective IgE deficiency is not known. Defects in immunoglobulin class switching have not been demonstrated conclusively (Roa *et al.*, 2008).

An elevated IgE level in blood serum is usually observed in either infections (worms, certain viruses, intracellular bacteria and protozoa) or allergic inflammation, but in some cases it can also occur during autoimmune disorders, immunodeficiency, graft-*versus*-host disease (GvHD) after transplantation and in several cancers (Table 1).

In worm infections (helminths, schistosomes, etc.), IgE and its receptors on effector cells serve as crucial components of host protective immunity. The infection induces a very pronounced humoral immune response with the production of antiparasite IgE antibodies, activation of mast cells, and recruitment of eosinophils that cause elimination of the parasites (Maizels *et al.*, 2009). On the other hand, elevated IgE production in response to pathogenic fungi and a range of intracellular pathogens (e.g. different species of *Leishmania*, etc.) is usually associated with disease progression and probably occurs due to the imbalance between different arms of the immune response (Brummer, Hanson & Stevens, 1993; Lucey, Clerici & Shearer, 1996; Lipoldová *et al.*, 2002; Havelková *et al.*, 2006).

Besides infectious agents, some apparently innocuous antigenic proteins of food, plants, fungi, etc. can provoke an allergic response that is characterized by elevated IgE production. The tendency to produce high levels of IgE against common environmental allergens is defined as atopy, and is often associated with the development of allergic diseases such as bronchial asthma, allergic rhinitis and atopic dermatitis.

Besides its stimulation by exogenous antigenic proteins IgE secretion can be stimulated also by some autoantigens, which are present in the human body under normal conditions. An example of this type of disorder is bullous pemphigoid disease (BP), which is a subepidermal blistering disease characterised by autoantibodies against the hemidesmosomal proteins bullous pemphigoid antigen 180, collagen, type XVII, alpha 1 (BP180) and dystonin (DST), a plakin family protein that anchors keratin filaments to hemidesmosomes). Specific IgEs to these proteins are often present in sera of patients (Arbesman *et al.*, 1974; Ishiura *et al.*, 2008). Elevated production of IgE was also observed in 35.5% of cases of hyperthyroid Graves' disease. The disease is characterised by the presence of polyclonal autoreactive T cells (Lipoldová *et al.*, 1989) and by the production of autoantibodies against thyroid stimulating hormone receptor (TSHR) (thyroid receptor antibodies, TRAb) leading to hyperthyroidism and goitre. Patients in which Graves' disease is accompanied by a high IgE level failed to develop remission after methimazole treatment in contrast with patients with a low IgE level (Yamada *et al.*, 2000).

Elevated IgE level can occur in the course of graft-*versus*-host disease (GvHD). Heyd *et al.* (1988) described this phenomenon in allogeneic, autologous and syngeneic (monozygous twin) bone marrow transplantation (BMT). IgE levels were found to be significantly increased in the allogeneic and syngeneic BMT recipients. Allogeneic BMT recipients displayed a biphasic elevation in serum IgE levels, with the peak occurring either early or late. IgE level correlated with clinical stage of GvHD only in individuals in whom peak levels occurred early. The association of IgE elevation and GvHD does not appear to be direct since the syngeneic recipients exhibited the highest IgE levels. It was supposed that increased IgE synthesis and its subsequent resolution is a consequence of immune reconstitution in the presence of potentially reagenic agents such as antibiotics and infectious agents. Mechanisms involved in GvHD have been also studied in mouse models. Hyperproduction of IgE in mice is associated with chronic stimulatory GvHD, and the enhanced secretion of IgE appears to be of host B cells origin, since (i) B cell-depleted donor spleen cells induced similar changes in IgE as whole spleen cells; and (ii) recipients depleted of B cells by whole-body irradiation did not develop hyper IgE (Doutrelepon *et al.*, 1991). Moreover, the hyper-IgE syndrome is modulated by cells of donor origin, such as donor CD8 T cells, which were found to enhance Th1 development and suppress IgE production during GvH reaction (Noble, Leggat & Inderberg, 2003).

High IgE levels were also described in several primary immunodeficiency disorders such as Wiskott-Aldrich syndrome; immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX); Omenn syndrome; atypical complete DiGeorge syndrome; and in the hyper-IgE syndrome (HIES) or Job's syndrome. Increased IgE levels in IPEX, Wiskott-Aldrich syndrome and Omenn syndrome are likely to be related to increased Th2 cytokine production caused by decrease in the numbers or functions of

Table 1. Pathological states associated with increased levels of immunoglobulin E (IgE)

Pathological state associated with elevated IgE level	Examples of diseases	Type of inheritance	Gene defects
Worm infections	Helminthes, schistosomes, etc.	Polygenic	
Intracellular pathogens	Different species of <i>Leishmania</i> , <i>Plasmodium falciparum</i> , etc.	Polygenic	
Allergic diseases	Atopic asthma, atopic dermatitis, rhinitis, etc.	Polygenic (see Table 2)	
Autoimmune diseases	Bullous pemphigoid disease, some cases of hyperthyroid Graves' disease	?	?
Immunodeficiencies	Hyper-IgE syndrome (HIES) HIES type 1	Autosomal dominant	<i>STAT3</i> mutations (Holland <i>et al.</i> , 2007; Minegishi <i>et al.</i> , 2007)
	HIES type 2	Autosomal recessive	<i>TYK2</i> (Minegishi <i>et al.</i> , 2006), <i>DOCK8</i> mutations (Engelhardt <i>et al.</i> , 2009)
	Wiskott-Aldrich syndrome	X-linked recessive	<i>WASP</i> mutations (Derry, Ochs & Francke, 1994)
	Omenn syndrome	Autosomal recessive	<i>RAG1</i> or <i>RAG2</i> (Villa <i>et al.</i> , 1998), <i>DCLRE1C</i> (Ege <i>et al.</i> , 2005), <i>IL-7R</i> (Giliani <i>et al.</i> , 2006), <i>RMRP</i> (Roifman <i>et al.</i> , 2006), <i>ζAP70</i> (Turul <i>et al.</i> , 2009), <i>ADA</i> (Roifman <i>et al.</i> , 2008), <i>DNA ligase IV</i> mutations (Grunebaum <i>et al.</i> , 2008), <i>IL2RG</i> (Gruber <i>et al.</i> , 2009)
	Comel-Netherton syndrome	Autosomal recessive	<i>SPINK5</i> mutations (Chavanas <i>et al.</i> , 2000)
	Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)	X-linked dominant	<i>FOXP3</i> mutations (Wildin <i>et al.</i> , 2001)
	Atypical complete DiGeorge syndrome	Autosomal dominant	22q11 hemizygosity (Driscoll, Budarf & Emanuel, 1992)
Tumours	Multiple myeloma, glioblastoma	?	?
Transplant rejection	Graft-versus-host disease	?	?

ADA, adenosine deaminase; *DCLRE1C* (*ARTEMIS*), DNA cross-link repair 1C; *DOCK8*, dedicator of cytokinesis 8; *FOXP3*, forkhead box P3; *IL-7R*, interleukin 7 receptor; *IL2RG*, interleukin 2 receptor, gamma; *RAG*, recombination activating gene; *RMRP*, RNA component of mitochondrial RNA processing endoribonuclease; *SPINK5*, serine peptidase inhibitor; *STAT3*, signal transducer and activator of transcription 3; *TYK2*, tyrosine kinase 2; *WASP*, Wiskott-Aldrich syndrome protein; *ζAP70*, zeta-chain (TCR) associated protein kinase.

CD4⁺CD25⁺forkhead box protein P3⁺ (Foxp3⁺) regulatory T cells (Ozcan, Notarangelo & Geha, 2008).

HIES is classified into type 1 and type 2. Patients with type 1 HIES have abnormalities of skeletal and connective tissue and suffer from recurrent staphylococcal infections that lead to pneumatocele. Patients with type 2 HIES have abnormalities of the immune system and are susceptible to viral and mycobacterial infections (Minegishi, 2009). However, it is not known whether the increase in IgE results from the inappropriate immune response to the pathogens or from the immune imbalance on its own. It was suggested that hyper IgE responses in HIES patients are of low affinity to environmental antigens and are derived by a direct switch $C\mu \rightarrow C\epsilon$ (Xiong *et al.*, 2012).

Some findings suggest that IgE is relevant for antitumour defence. IgE can arm monocytes and eosinophils for antitumour activity (Karagiannis *et al.*, 2007). In multiple myeloma patients the IgE level is strongly associated with survival prognosis: myeloma patients with elevated polyclonal IgE levels (> 100 IU/ml) had 2–3 years longer survival than those with low (< 10 IU/ml) or intermediate

(10–100 IU/ml) values (Matta *et al.*, 2007). Glioblastoma patients with elevated IgE had 9 months longer survival than those with normal or borderline IgE levels (Wrensch *et al.*, 2006). Genetic polymorphisms in Fc receptor IgE high-affinity 1 and 2 (*FCER1* and *FCER2*) were reported to be associated with breast (Lee *et al.*, 2009b) and lung (Shen *et al.*, 2009) cancer risk, respectively.

IV. GENETIC REGULATION OF IgE LEVEL

(1) Genetic regulation of IgE level in humans

The level of IgE secretion is dependent on environmental stimuli, of which the most important are the frequency and route of exposure to IgE-stimulating antigens (allergens, infectious agents, autoantigens, etc.), exposure to irritants such as air pollutants and tobacco smoking, which may weaken an organism and/or increase the immunogenic capacity of antigens, and social/life-style conditions including diet. Environmental stimuli might also exert epigenetic effects

(Prescott & Saffery, 2012). Certain individual characteristics determine a person's type of reaction to the environmental stimuli he or she is exposed to. Multiple segregation analyses, pedigree- and twin-based studies show high heritability of IgE level (both total and specific) indicating that genetic factors are likely to have an impact on IgE regulation (Dizier *et al.*, 1999; Sampogna *et al.*, 2000; Jacobsen *et al.*, 2001; Palmer *et al.*, 2001; Strachan, Wong & Spector, 2001; Mathias *et al.*, 2005; Grant *et al.*, 2008). However, the mode of the genetic regulation of IgE seems to be different in various pathologies. In allergic and infectious diseases, IgE is likely to be influenced by a pattern of polymorphisms in multiple interacting genes as demonstrated in studies both in humans and in mouse models (see Section IV). Moreover, it has been observed that IgE-controlling loci often vary in different human populations, supporting the possibility of several at least partly different mechanisms of genetic regulation of IgE depending on genetic background. Another type of genetic regulation was revealed for example in HIES type 1 and 2, and depends on mutations in single genes. HIES type 1 is inherited as sporadic (more than 90% of cases) or familial with autosomal dominant inheritance, whereas HIES type 2 shows only familial autosomal recessive inheritance (described in Section IV.1c and Table 1) (Minegishi *et al.*, 2006; Holland *et al.*, 2007; Engelhardt *et al.*, 2009; Minegishi, 2009).

(a) Genetic loci and genes controlling IgE in humans with atopy

To search for IgE-controlling loci and genes in humans and to investigate their biological role in the development of allergic diseases, several strategies have been developed. They include the candidate-gene approach, genome-wide linkage and association mapping, and recently module-based analysis.

The candidate-gene approach (hypothesis-driven) selects candidate genes on the basis of *a priori* knowledge of the trait/disease of interest (biological candidates) or of candidate-gene regions (positional candidates) previously linked to the trait of interest. The method includes association studies that test the role of specific polymorphisms (single nucleotide polymorphisms—SNPs and/or short tandem repeat—STR markers) in candidate genes or genetic loci. These studies can be either population-based (case-control) or family-based (transmission disequilibrium test). Genes encoding proinflammatory cytokines and other molecules that code proteins with functional relevance for IgE production were high-priority candidates in studies of the genetics of atopy. Association of polymorphisms in interleukin 13 (*IL13*) (5q31.1) with total serum IgE was the most frequently corroborated (Graves *et al.*, 2000; Donfack *et al.*, 2005; Maier *et al.*, 2006; Beghe *et al.*, 2010); *IL13* was also associated with levels of several specific IgEs (Liu *et al.*, 2004; Donfack *et al.*, 2005). Polymorphisms in genes *IL4* (5q31.1) (Basehore *et al.*, 2004), receptor for IL-4 (*IL4RA*) (16p12.1-p11.2) (Mitsuyasu *et al.*, 1999), signal transducer and activator of transcription 6 (*STAT6*, 12q13) (Schedel *et al.*, 2009) showed significant association with level of total IgE in

various populations. Moreover, it was shown that interactions between different polymorphisms in the *IL4/IL13* pathway composed of *IL4*, *IL13*, *IL4Ra*, and *STAT6* influence the genetic control of total serum IgE level during allergic bronchial asthma (Kabesch *et al.*, 2006). Polymorphisms in the candidate genes interleukin 1 receptor antagonist gene (*IL1RN*) (chromosome 2q14.2) (Pattaro *et al.*, 2006), *IL6* (7p21) and *IL18* (11q22.2-q22.3) (Imboden *et al.*, 2006), tumor necrosis factor α (*TNFA*) (6p21.3) (Sharma *et al.*, 2006), interferon γ (*IFNG*) (12q14) (Nagarkatti *et al.*, 2002), nitric oxide synthase 1 (*NOS1*) (12q24.2-q24.31) (Immervoll *et al.*, 2001; Holla *et al.*, 2004; Leung *et al.*, 2005) and polymorphism in mitochondrial DNA (European mitochondrial haplogroup U) (Raby *et al.*, 2007) were also associated with total IgE level. However, the limitation of our knowledge about IgE regulatory mechanisms makes it impossible to predict all genes that might be involved in this regulation. This is the major limitation of the candidate locus/gene approach.

Alternatively, genome-wide screens allow previously unrecognised genes to be identified in a hypothesis-independent manner. Genome-wide linkage studies, which might be model-based (inheritance pattern, extended family studies) or model-free (sibling pairs), attempt to identify patterns of co-segregation of the analysed traits and polymorphic markers to identify loci and subsequently the genes controlling these traits. In the genome-wide scans for atopy and IgE-controlling loci in humans the most common linkages were detected in chromosomal regions 5q (Xu *et al.*, 2000; Yokouchi *et al.*, 2000, 2002; Haagerup *et al.*, 2002; Koppelman *et al.*, 2002), 6p (Daniels *et al.*, 1996; Wjst *et al.*, 1999; Haagerup *et al.*, 2002; Ferreira *et al.*, 2005), 7p (Daniels *et al.*, 1996; Laitinen *et al.*, 2001; Shugart *et al.*, 2001; Altmuller *et al.*, 2005), 7q (Xu *et al.*, 2000; Koppelman *et al.*, 2002; Altmuller *et al.*, 2005), 11q (Daniels *et al.*, 1996; Shugart *et al.*, 2001; Altmuller *et al.*, 2005), 12q (Xu *et al.*, 2000; Koppelman *et al.*, 2002; Yokouchi *et al.*, 2002) and 16q (Daniels *et al.*, 1996; Ober *et al.*, 2000; Kurz *et al.*, 2005). The positional cloning approach (genome-wide scans for susceptibility loci and a subsequent fine-mapping of the genes) indicated three genes at loci 2q33 (cytotoxic T-lymphocyte-associated-4 gene, *CTLA4*) (Howard *et al.*, 2002), 7p14.3 (G protein-coupled receptor, *GPR4*) (Laitinen *et al.*, 2004), and 13q14 (PHD finger protein 11, *PHF11*) (Zhang *et al.*, 2003), predisposing to atopy and atopy-associated traits (Table 2).

In the past decade, the success of the International HapMap Project started a new phase in human genetics (McVean, Spencer & Chaix, 2005). Characterisation of patterns of genetic variation through typing about 4 million SNPs in DNA from populations with African, Asian, and European ancestry (<http://hapmap.ncbi.nlm.nih.gov/>), calculation of linkage disequilibrium between them and construction of comprehensive maps of SNP haplotypes provided an unprecedented view of human genetic diversity and has become a powerful tool for genome-wide association studies (GWAS) of complex traits in humans. The genome-wide scan for total serum IgE revealed genes *FCER1A* (Fc fragment of IgE, high affinity I, receptor for;

Table 2. Human genes controlling immunoglobulin E (IgE) level detected in genome-wide studies^a

Locus	Gene	Gene name	Possible effects of the gene	Trait controlled	References
1q23.2	FCERIA	Fc fragment of IgE, high affinity I, receptor for alpha polypeptide	Regulation of total IgE level	Total IgE , allergic sensitisation	Granada <i>et al.</i> (2012) and Weidinger <i>et al.</i> (2008)
2q33	CTLA4	Cytotoxic T-lymphocyte-associated-4 gene	Regulation of T cell activation	Total IgE , asthma, BHR	Howard <i>et al.</i> (2002)
5q22.1	TMEM232^b and SLCA25A46^b	transmembrane protein 232; solute carrier family 25, member 46	?	Specific IgE , (allergic rhinitis) ^o	Ramasamy <i>et al.</i> (2011)
5q31.1	RAD50^c and IL13^c	RAD50 homolog (<i>S. cerevisiae</i>); interleukin 13	Regulation of Th2 cytokine gene transcription; regulation of total IgE level	Total IgE , atopic eczema, asthma	Granada <i>et al.</i> (2012) and Weidinger <i>et al.</i> (2008)
6p21.3	HLADRB1	Major histocompatibility complex, class II, DR beta 1	Antigen presentation	Total IgE	Moffatt <i>et al.</i> (2010)
6p21.3	HLADRB4	Major histocompatibility complex, class II, DR beta 4	Antigen presentation	Specific IgE	Ramasamy <i>et al.</i> (2011)
7p14.3	GPRA	Neuropeptide S receptor 1	?	Total IgE , BHR, allergic asthma	Laitinen <i>et al.</i> (2004)
8q22	ANKRD46	Ankyrin repeat domain 46	?	Specific IgE	Wan <i>et al.</i> (2011)
11q13.5	C11orf30 or LRRC32	Chromosome 11 open reading frame 30; leucine-rich repeat-containing 32	?	Specific IgE , allergic rhinitis	Ramasamy <i>et al.</i> (2011)
12q13.3	STAT6	Signal transducer and activator of transcription 6, interleukin-4 induced	Regulation of total IgE level	Total IgE	Granada <i>et al.</i> (2012) and Weidinger <i>et al.</i> (2008)
13q14	FNDC3A	Fibronectin type III domain containing 3A	?	Specific IgE	Wan <i>et al.</i> (2011)
13q14.3	PHF11^d	PDH finger protein 11	Regulation of total IgE level	Total IgE , allergic asthma,	Zhang <i>et al.</i> (2003)
	SETDB2^d	SET domain, bifurcated 2	Regulation of total IgE level	Total IgE , allergic asthma	Zhang <i>et al.</i> (2003)
	RCBTB1^d	Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1	?	Total IgE , allergic asthma	Zhang <i>et al.</i> (2003)

^aOnly the genes with the genome-wide $P < 5 \times 10^{-7}$ are listed.

^bDue to the close proximity of *TMEM232* and *SLCA25A46* genes, their role in regulation of total IgE level and asthma is still not clearly elucidated.

^cDue to the close proximity of *RAD50* and *IL13* genes authors could not differentiate the source of the association signal.

^dDue to the close proximity of *PHF11*, *SETDB2* and *RCBTB1* genes, their role in regulation of total IgE level and asthma is still not clearly elucidated.

BHR, bronchial hyperresponsiveness; Th2, T helper 2 cell.

alpha polypeptide) at locus 1q23, RAD50 homolog (*S. cerevisiae*) (*RAD50*) at locus 5q31, *STAT6* at locus 12q13 (Weidinger *et al.*, 2008), and major histocompatibility complex, class II, DR beta 1 (*HLADRB1*) at locus 6p21.3 (Moffatt *et al.*, 2010). Chromosome 11 open reading frame 30 (*C11orf30*) or leucine-rich repeat containing 32 (*LRRC32*) at 11q13.5, and transmembrane protein 232 (*TMEM232*) and solute carrier family 25, member 46 (*SLCA25A46*) at 5q22.1 were associated with both grass-sensitisation and

allergic rhinitis, whereas major histocompatibility complex, class II, DR beta 4 (*HLADRB4*) at 6p21.3 was associated with grass-sensitisation only (Ramasamy *et al.*, 2011). A genome-wide association study in the British 1958 birth cohort found association of ankyrin repeat domain 46 (*ANKRD46*) and fibronectin type III domain containing 3A (*FNDC3A*) at 8q22 and 13q14, respectively, with specific IgE to at least one allergen including house dust mites, mixed grass, or cat fur (Wan *et al.*, 2011) (Table 2).

Another approach for identification of novel genes associated with allergy is a module-based analytical strategy. The module-based analysis is an arrangement of disease-associated genes in modules based on co-expression data and known gene interactions followed by a search for novel genes related to the modules with subsequent validation of the genes by functional analysis. Using this approach, the gene encoding the receptor for IL-7 (*IL7R*) was identified as relevant for the development of several allergic diseases (Mobini *et al.*, 2009).

(b) *Genetic loci and genes controlling IgE in studies of human infectious diseases*

Although IgE is an inherent participant of the immune response to many infectious agents, there are only a few studies of genetic regulation of IgE during infectious diseases in humans. In the genome-wide scan for quantitative-trait loci influencing susceptibility to the parasite *Ascaris lumbricoides* in a Jirel population (Nepal), the locus 13q33-34 was significantly linked to *A. lumbricoides* egg counts and showed suggestive linkage to total IgE level (Williams-Blangero *et al.*, 2002). Subsequent candidate-gene study on this locus revealed association of polymorphism in ligase IV (*LIG4*) with specific IgE to *Ascaris* extract and of the tumor necrosis factor (ligand) superfamily, member 13b (*TNFSF13B*) with IgE to *Ascaris* body fluid allergen (ABA-1) (Acevedo *et al.*, 2009). In another genome-wide search in a Costa Rican population, *Ascaris*-specific IgE showed linkage to a locus on chromosome 7q35 (Hunninghake *et al.*, 2008). Candidate-gene study of *A. lumbricoides* infection in a Venezuelan cohort revealed that polymorphisms in the gene for beta-2-adrenoreceptor (*B2AR*, 5q31-q32) were associated with *Ascaris*-specific IgE (Ramsay *et al.*, 1999), whereas in patients with *A. lumbricoides* infection from a Chinese population, haplotypes of *STAT6* (12q13) were associated with total IgE (Moller *et al.*, 2007). In the genome-wide study of multi-case leprosy caused by parasite *Mycobacterium leprae* in a Belém population of Brazil, the locus 2q12.1 showed linkage to total IgE (Wheeler *et al.*, 2006). A candidate-gene approach revealed polymorphisms in the *IL1RN* (2q14.2) in a Tanzanian population (Carpenter *et al.*, 2007) and *IL4* (5q31.1) in ethnic groups from Burkina Faso and Mali associated with total IgE during *Plasmodium falciparum* infection (Verra *et al.*, 2004; Carpenter *et al.*, 2007; Vafa *et al.*, 2009). IgE might play an important role in cerebral malaria, as C57BL/6 mice genetically deficient for the high-affinity receptor for IgE (*Fcer1a*) (chromosome 1) or for IgE (*Igh-7*) (chromosome 12) were less susceptible to experimental cerebral malaria after infection with *Plasmodium berghei* (Porcherie *et al.*, 2011).

(c) *Genes controlling hyper-IgE syndrome in humans (HIES)*

Studies of the etiology of HIES were originally quite contradictory as both autosomal dominant and recessive inheritance was reported. Recently, two types of the disorder were discriminated depending on differences in clinical manifestation and genetic etiology (Minegishi *et al.*, 2006; Holland *et al.*, 2007; Minegishi, 2009) (Table 1).

Type 1 HIES is characterised by skeletal and dental abnormalities, susceptibility to predominantly pulmonary infection leading to pneumatoceles and elevated IgE level. Coronary artery aneurysms and tortuosity are also common (Freeman *et al.*, 2011). This disease results from mismatch mutations and single-codon in-frame deletions in signal transducer and activator of transcription 3 gene (*STAT3*). These mutations can appear sporadically or can be transmitted/inherited in autosomal dominant fashion and are often located in DNA-binding, Src-homology 2 (SH2), linker and transactivation domains (Holland *et al.*, 2007; Minegishi *et al.*, 2007; Woellner *et al.*, 2010). The defects in *STAT3* result in impaired differentiation of Th17 cells. It was shown that the production of antistaphylococcal factors by primary human keratinocytes and bronchial epithelial cells is particularly dependent on Th17 cytokines (IL-17A, IL-17F and IL-22). This explains the restriction of the infection to the skin and lungs (Minegishi *et al.*, 2009). Coronary artery abnormalities in *STAT3*-mutated HIES patients suggest that *STAT3* also plays an integral role in human vascular remodelling and atherosclerosis (Freeman *et al.*, 2011).

Type 2 HIES is less prevalent and is characterised by abnormalities in the immune system and susceptibility to viral infections (e.g. molluscum contagiosum and herpes simplex virus) as well as by hyperproduction of IgE. Polymorphisms in two genes inherited in the monogenic autosomal-recessive manner were identified as a cause of the disease. Tyrosine kinase 2 (*TYK2*) is a member of Janus kinase family (JAKs) proteins that transduce signals downstream from a number of cytokines. Patients homozygous for the deletion in *TYK2* display normal T cell receptor (TCR) signaling but signal transduction from IL-12, IFN α and some other cytokines, particularly IL-6, IL-10, and IL-23 is abrogated. It is assumed that the resulting predominance of Th2 over Th1 response may lead to elevated production of IgE and atopic dermatitis-like skin inflammation in HIES patients (Minegishi *et al.*, 2006). Other patients with type 2 HIES were homozygous for autosomal-recessive mutations in dedicator of cytokinesis 8 (*DOCK8*). The biological functions of *DOCK8* include regulation of cell migration, morphology, adhesion and growth (Meller, Merlot & Guda, 2005) and it also acts as an adaptor that links toll-like receptor 9 (TLR9)–MyD88 (myeloid differentiation primary response 88) signalling to B cell activation (Jabara *et al.*, 2012). *DOCK8* deficiency is associated with impaired activation of CD4⁺ and CD8⁺ T cells (Engelhardt *et al.*, 2009; Zhang *et al.*, 2009), impaired antibody responses and fewer CD27⁺ memory B cells (Jabara *et al.*, 2012). In mouse, *Dock8*-mutant B cells are unable to persist in GCs and undergo affinity maturation (Randall *et al.*, 2009). However, it is still not clear which of these pathways are engaged in the elevation of IgE level during HIES.

(d) *Genetic regulation of IgE during Graves' disease*

Using the candidate-gene approach, polymorphic variants of *IL13* (5q31.1) (Chong *et al.*, 2008), *IL4RA* (16p12.1-p11.2) and *STAT6* (12q13) (Yabiku *et al.*, 2007; Chong *et al.*, 2008)

showed association with total IgE during Graves' disease, but *IL13* association became insignificant after Bonferroni correction (Chong *et al.*, 2008). IL-4R α chain is shared by IL-4R and IL-13R. Once IL-4 or IL-13 activates these receptors, activation by IL-4R α leads to phosphorylation of STAT6 with the consequent induction of IgE secretion (Lin *et al.*, 1995).

Polymorphisms in *STAT6* controlling IgE level were revealed in genome-wide association studies of human atopic diseases (Weidinger *et al.*, 2008; Granada *et al.*, 2012), and in association studies of human atopy (Kabesch *et al.*, 2006; Schedel *et al.*, 2009) and infection with *Ascaris lumbricoides* (Moller *et al.*, 2007) (see Sections IV.1a–c), thus indicating involvement of this pathway in autoimmune, atopic and infectious diseases.

(2) Genetic regulation of IgE level in mouse

(a) Genetic approaches to identification of mouse genes responsible for IgE level

There has been remarkable progress in the identification of a large number of IgE-controlling genes in human studies. However, the complete elucidation of the genetics of inappropriate IgE production in humans is hindered by many factors including sample size, genetic heterogeneity of human populations, gene interactions, low frequency and/or incomplete penetrance of trait-controlling alleles and a high variability of environmental factors (Lander & Schork, 1994). Some limitations of human genetic studies can be overcome or complemented by the use of mouse models. The availability of genetically homogenous mouse strains (inbred strains), the possibility to manipulate the mouse genome through selective breeding strategies, along with direct gene-targeting approaches and the ability to control the environment to reduce phenotypic variance, gives mouse models considerable power to predict complex traits/disease susceptibility genes in humans (Lipoldová & Demant, 2006). Once the genetic regions of interest are identified in the mouse, the high level of synteny between many mouse and human chromosomal regions allows predictions of their locations in humans (DeBry & Seldin, 1996). Although the application of mouse models to humans is not always straightforward, they represent a powerful complementary strategy for investigation of genetic and environmental components of complex traits in humans.

Mouse genetic studies of IgE regulation under various conditions use a range of breeding strategies. Generating F₂ hybrids between inbred strains (IS) allows mapping of loci involved in the control of complex genetic traits. However, the mapping resolution is rather low due to the low number of recombinations, which should be compensated by a large number of progeny in the F₂ population analysed (Darvasi, 1998). This problem can be overcome in advanced intercross lines (AIL), which are produced by intercrossing F₂ hybrids between two inbred strains avoiding mating brother $\times$ sister. The accumulation of recombinations in AILs reduces linkage disequilibrium and thus provides a high mapping resolution (Darvasi & Soller, 1995; Behnke *et al.*, 2006).

In a different breeding protocol, randomly chosen F₂ hybrids are mated brother $\times$ sister for at least 20 generations. The protocol yields recombinant inbred strains (RIS), which each possess a different random portion of 50% of the genome of each parental strain in homozygous state (Bailey, 1971). The comparison of phenotypes of RIS was successfully used for mapping complex traits (Bailey, 1971; Nicolaides *et al.*, 1997); the panel of RIS, however, should be sufficiently wide as each single RIS represents a single genotype in this type of analysis.

Another strategy, which is based on reducing the amount of the donor strain genome relative to the background strain genome, is applied in recombinant congenic strains (RCS). RCS are produced by mating two inbred strains, backcrossing their descendants to one of the parental strains, usually for two generations, with subsequent brother $\times$ sister inbreeding for about 20 generations. The protocol yields a panel of RCS each bearing a random 12.5% of the donor parental strain genome on the background of the other parental strain genome (Demant & Hart, 1986). The influence of donor-strain-derived segments is studied separately in F₂ hybrids between selected RCS and background parental strain (Lipoldová *et al.*, 2000; Badalová *et al.*, 2002; Kurey *et al.*, 2009).

Finally, congenic strains may be generated by multiple backcrosses selective for a given locus, which allows characterisation of this locus without interference from multiple epistatic genes that also influence a phenotype (McIntire *et al.*, 2001). This breeding can be highly facilitated by using the speed congenic approach (Markel *et al.*, 1997). There are also other genetic systems such as chromosome substitution strains (Nadeau *et al.*, 2000) and the collaborative cross (Threadgill, Hunter & Williams, 2002), but they have not yet been used for the study of the genetic regulation of IgE level.

The precise mapping of genes within known candidate loci can be accomplished using panels of mice transgenic for yeast artificial chromosomes (YAC), which are vectors with large insert size. They provide a possibility to generate mice transgenic for up to 1000 kb long genome segments containing multiple genes and regulatory elements (Schedl *et al.*, 1993). Bacterial artificial chromosomes (BAC) (Cai *et al.*, 2001) and P1-derived artificial chromosomes (PAC) (Ioannou *et al.*, 1994), which carry inserts of 200–300 kb are also valuable mapping tools (Copeland, Jenkins & Court, 2001) and have been used successfully for analysis of the IL-4 cytokine family gene cluster on mouse chromosome 11 (Wenderfer *et al.*, 2000) that is homologous with the human 5q31-q33 segment involved in regulation of IgE (Xu *et al.*, 2000).

To assess the role of individual candidate genes, mice transgenic for a single gene are used. To study the gain of function, transgenes are designed to carry an active allelic variant of the protein, to be overexpressed or to be expressed conditionally in an informative developmental stage or cell type (Branda & Dymecki, 2004). To study the loss of function, mice transgenic for an inoperative candidate

gene (knocked-out gene) are used. If the knock-out leads to embryonic lethality, the target gene can be knocked out conditionally—only in selected organs or cells, or at certain stages of development. Alternatively, a dominant-negative allele can be introduced, which is expressed tissue-specifically (Zhang *et al.*, 1999). Finally, the loss of function can be studied using gene knock-down through RNA interference (Shan, 2010). Silencing IL-23 expression by a small hairpin RNA significantly decreased the serum levels of IL-23, IgE, IL-17, and IL-4 and protected ovalbumin (OVA)-sensitised BALB/c-strain mice against asthma (Li *et al.*, 2011).

(b) *Identification of IgE-controlling genes in mouse models of allergic asthma, allergic rhinitis and atopic dermatitis*

The murine models of allergic asthma are usually based on sensitisation with an antigen followed by an antigen challenge (Table 3). An elevated IgE level and other asthma-associated traits such as airway hyperresponsiveness (AHR), airway eosinophilia, and pulmonary inflammation represent the most common phenotypic traits in these models.

Mouse chromosomal segments homologous to human atopy locus 5q31-q33 (Postma *et al.*, 1995; CSGA, 1997; Nicolaides *et al.*, 1997) were especially extensively investigated in mouse. The region corresponds to syntenic segments on mouse chromosomes 11, 13 and 18. The fine mapping of the regions was performed in a panel of 26 recombinant inbred strains derived from hyporesponsive C57BL/6J and hyperresponsive DBA/2J mouse strains in the model of stimulation with a bronchoconstrictor agent atracurium. Linkage to AHR was obtained only for the segment containing *Il9* gene on mouse chromosome 13 (Nicolaides *et al.*, 1997). For the further analysis, FVB/NJ mice transgenic for an additional copy of *Il9* (FVB/N-TG5) were generated. Challenged with *Aspergillus fumigatus* antigen, FVB/N-TG5 mice showed a much higher serum IgE level, AHR and high eosinophil numbers in bronchoalveolar lavage in comparison with wild-type mice (McLane *et al.*, 1998).

In another study, the mouse ortholog to the human 5q31 chromosomal region was dissected using FVB/N mice transgenic for a panel of YACs covering the human 5q31 locus. Strains bearing YAC854G6 and YAC854G6-F1, which overlap in the segment carrying human *IL4* and *IL13* genes, but not YAC131F9 [carrying colony-stimulating factor 2 (*CSF2*) and *IL3*] had significantly reduced serum IgE levels in response to sensitisation and subsequent challenging with chicken ovalbumin (OVA). The transgenic mice, four times backcrossed to BALB/c, expressed human *IL4* and *IL13* genes instead of mouse *Il4* and *Il13* genes, which were expressed at much lower rates than in wild-type mice. Products of human *IL4* and *IL13* genes are inactive in mice, thus the lack of mouse IL-4 and IL-13 resulted in the attenuation of the allergic phenotype. FVB/N mice transgenic for a bacterial artificial chromosome (BAC) containing additional copies of mouse *Il4* and *Il13* genes displayed increased serum total IgE, a bronchoconstrictor response and inflammatory cell counts after sensitisation and subsequent challenging with OVA (Symula *et al.*, 1999).

Mouse models were also successfully used for the assessment of the role of several candidate genes of atopy and allergic asthma. The tested genes were either knocked out or suppressed through the expression of a dominant-negative allele. The alterations resulted in an impaired IgE response and different degrees of recovery from the atopic phenotype in the model of sensitisation and subsequent challenge with OVA or other antigens (Table 3) (Fig. 1). The involvement of a number of studied genes [e.g. *Il4*, *Il13*, *Fcer1a*, *Fcer2a/Cd23*, T-box 21 (*Tbx21/Tbet*), *Cd40*, suppressor of cytokine signaling 1 (*Socs1*), Yamaguchi sarcoma viral (v-yes-1) oncogene homolog (*Lyn*), inducible T-cell co-stimulator (*Icos*), *Stat6*, *Cd80*, *Cd86*, GATA binding protein 3 (*Gata3*), cellular reticuloendotheliosis oncogene (*c-Rel/Rel*) in IgE regulation could have been predicted from previous knowledge of their functions in lymphocyte development, differentiation, activation and proliferation, whereas the role of the other genes in IgE regulation e.g. NIPA (the non-imprinted in Prader-Willi/Angelman syndrome)-like domain containing 3 (*Npal3*), transient receptor potential cation channel, subfamily C, member 6 (*Trpc6*), arachidonate 15-lipoxygenase (*Alox15*), lectin, galactose binding, soluble 3 (*Lgals3*), sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain (semaphorin) 4B (*Sema4b*), Epstein-Barr virus induced gene 3 (*Ebi3*), inositol polyphosphate-5-phosphatase D (*Inpp5d*), and neurturin (*Nrtn*)] was less obvious before the analysis of knock-out or modified genes in mouse models (Table 3) (Fig. 1).

Interestingly, deletion of *Il27ra* led to a different outcome in models of allergic rhinitis and asthma. *Il27ra*^{-/-} mice developed augmented immune responses in the serum (IgE production), cervical lymph nodes (cytokine and chemokine expression), and nasopharynx-associated lymphoid tissues (cytokine and chemokine expression), whereas local responses of allergic rhinitis, such as sneezes and nasal rubs, and nasal lavage fluid cytokine production, were reduced (Shimanoe *et al.*, 2009).

Comparison of inhibitor of DNA binding/ differentiation 2 (*Id2*)^{-/-} and *Id2*^{+/-} animals exposed to OVA in the mouse model of allergic rhinitis showed different regulation of production of total and specific IgE. *Id2*^{-/-} mice had higher levels of total serum IgE than *Id2*^{+/-}, whereas *Id2*^{+/-} produced more serum OVA-specific IgE than *Id2*^{-/-} animals (Kim *et al.*, 2012). Similarly, in human studies some specific IgEs are significantly related to high total IgE, whereas other IgEs do not make a significant contribution to high total IgE (Erwin *et al.*, 2007; Gusareva *et al.*, 2008).

Several mouse strains with a spontaneously occurring atopic dermatitis-like phenotype (NC/Nga, NOA, DS-Nh) have been described. To date, a gene causing the elevation of IgE level has been defined only for the DS-Nh strain which was derived from a mutant mouse in an inbred DS strain colony. DS-Nh mice exhibit a hairless phenotype, spontaneous dermatitis and elevated serum IgE levels under conventional conditions. It was reported that

Table 3. Genes controlling serum immunoglobulin E (IgE) level in mouse models of allergic asthma, allergic rhinitis and atopic dermatitis

Chr./cM	Tested gene	Genetic modification	Genetic background	Stimulation	Phenotype in comparison with wild type	References
1/6.45	<i>Il17a</i>	<i>Il17a</i> ^{-/-}	BALB/c	OVA ^S , SPF conditions	Decrease in serum IgE levels, and in eosinophil infiltration into the nasal mucosa	Quan <i>et al.</i> (2012)
1/18.81	<i>Il1r1</i>	<i>Il1r1</i> ^{-/-}	<i>Il1r1</i> ^{-/-} - C57BL/6 mice after transfer of lymph node T cells from OT-II mice	OVA plus LPS, SPF conditions	Strikingly higher serum IgE, induced by increase of the proportion of cytokine-producing transgenic CD4 T cells after exposure to IL-1	Ben-Sasson <i>et al.</i> (2009)
1/19.19	<i>Il1r1</i> (S12)	<i>Il1r1</i> ^{-/-}	BALB/c	OVA ^S , SPF conditions	Lower OVA-specific IgE, reduced eosinophil and macrophage counts in BAL fluids	Morita <i>et al.</i> (2012)
1/26.81	<i>Stat1</i>	<i>Stat1</i> ^{-/-}	BALB/c	SEA sensitisation, SPF conditions	Lower SEA-specific IgE, impaired nasal eosinophilia and markedly reduced histamine-induced nasal hyperresponsiveness	Hattori <i>et al.</i> (2007)
1/30.52	<i>Cd28</i>	<i>cd28</i> ^{-/-}	C57BL/6	Immunisation with <i>S. mansoni</i> eggs and challenge with SEA, SPF conditions	Abolished total IgE production, greatly (more than 90%) reduced BAL eosinophilia	Mathur <i>et al.</i> (1999)
1/30.6	<i>Icos</i>	<i>Icos</i> ^{-/-}	C57BL/6	Immunization with <i>S. mansoni</i> eggs and challenge with SEA, SPF conditions	Lower total IgE, PE, less CD4 ⁺ T cells in the BAL after sensitisation and challenge	Shilling <i>et al.</i> (2009)
1/44.44	<i>Inpp5d</i>	<i>Inpp5d</i> ^{-/-}	BALB/c	OVA ^S , SPF conditions	Diminished serum OVA-specific IgE, less cell infiltration around the airways but more in the parenchyma, less mucus production	Roongapinun <i>et al.</i> (2010) and Kuroda <i>et al.</i> (2011)
1/57.14	<i>Ctse</i> (<i>Cate</i>)	<i>Ctse</i> ^{-/-}	C57BL/6	no stimulation, SPF conditions	≈fourfold elevated serum IgE, twice as many splenic CD4 ⁺ Th2 cells	T sukuba <i>et al.</i> (2003)
1/63.84	<i>Ptgs2</i> (<i>Cox-2</i>)	<i>Ptgs2</i> ^{-/-}	C57BL/6 × 129/SvJae	No stimulation, SPF conditions	Higher total IgE, dermatitis	Laouini <i>et al.</i> (2005)
1/78.02	<i>Fcγ2b</i>	<i>Fcγ2b</i> ^{-/-}	C57BL/6 × 129/SvImJ	OVA ^E , SPF conditions	Higher OVA-specific IgE and lower OVA-specific IgG2a levels	Watanabe <i>et al.</i> (2004)
1/80.33	<i>Fcγ1a</i> (<i>Fcγ1</i>)	<i>Fcγ1a</i> ^{-/-}	BALB/c	Intranasal, intraperitoneal and passive SEA sensitisation, SPF conditions	Lower specific IgE, high PE and nasal mucosa secretion	Abboud <i>et al.</i> (2009)
2/6.69	<i>Gata3</i>	<i>Gata3</i> ^{-/-} (inducible, T-cell specific)	(C57BL/6 × SJL)F ₂ × BALB/c	OVA ^E , SPF conditions	Lower total and OVA-specific IgE; decrease of skin inflammatory response; increase of the expression of IL-10 and Foxp3 after OVA sensitisation	Zhang <i>et al.</i> (1999)

Table 3. Continued

Chr./cM	Tested gene	Genetic modification	Genetic background	Stimulation	Phenotype in comparison with wild type	References
2/85.16	<i>Sipi</i>	<i>Sipi</i> ^{-/-} ; <i>Sipi</i> Tg mice (OVA-induced SLPI overexpression)	C57BL/6	OVA ^S , SPF conditions	<i>Sipi</i> ^{-/-} mice showed higher total IgE, AHR, airway eosinophilia; <i>Sipi</i> Tg mice—lower total IgE, AHR, and airway eosinophilia	Marino <i>et al.</i> (2011)
2/85.38	<i>Cd40</i>	<i>Cd40</i> ^{-/-}	129S4/SvJae	No stimulation, stimulation with TD and TI Ags	Absence of serum IgE, severely decreased IgG1 and IgG2a; impaired germinal centres formation following immunisation with TD Ags	Castigli <i>et al.</i> (1994)
2/88.91	<i>Nfatc2</i> (<i>NEAT1</i>)	<i>Nfatc2</i> ^{-/-}	C57BL/6 × 129/Sv	OVA ^S	Higher total IgE and IL-4; lower IFN γ ; increased in airway eosinophilia after OVA sensitisation	Fonseca <i>et al.</i> (2009)
3/18.36	<i>Il21</i>	<i>Il21</i> ^{-/-}	C57BL/6 × 129/Sv	No stimulation, OVA ^I , SPF conditions	Higher total IgE without stimulation, increased total and OVA-specific IgE response under OVA stimulation	Shang <i>et al.</i> (2006)
3/25.46	<i>Postn</i>	<i>Postn</i> ^{-/-}	129Sjv × C57BL/6 mice backcrossed to C57BL/6 (F3 or F6 generation)	Intranasal immunisation with <i>Aspergillus fumigatus</i> , SPF conditions	Higher total IgE and AHR following allergen challenge; decreased expression of TGF- β 1 and Foxp3 in the lungs	Gordon <i>et al.</i> (2012)
3/37.4	<i>Th2</i>	<i>Th2</i> ^{-/-}	C57BL/6	Exposure to NO ₂ , OVA ^S	Lower OVA-specific IgE, decreased airway eosinophilia	Bevelander <i>et al.</i> (2007)
3/40.74	<i>Amt</i> (<i>HIF-1β</i>)	<i>Amt</i> ^{-/-}	C57BL/6	OVA ^S	Diminished production of OVA-specific IgE and IgG ₁ , reduced allergic response in the lung	Huerta-Yepez <i>et al.</i> (2011)
3/41.72	<i>Fcgr1</i>	<i>Fcgr1</i> ^{-/-}	BALB/c	OVA ^E , SPF conditions	Lower total and OVA-specific IgE; no dermatitis; increase in expression of IL-10 and Foxp3 after OVA sensitisation	Abboud <i>et al.</i> (2009)
4/2.05	<i>Lyn</i>	<i>Lyn</i> ^{-/-}	SV129 × C57BL/6	PSA	Higher total IgE, increase of circulating histamine, higher dermal mast cell numbers	Odom <i>et al.</i> (2004)
4/16.28	<i>Cnr1</i>	<i>Cnr1</i> ^{-/-} / <i>Cnr2</i> ^{-/-}	C57BL/6	OVA ^S	Lower OVA-specific IgE and attenuation of neutrophilia in BAL fluid	Kaplan <i>et al.</i> (2010)
4/68.01	<i>Cnr2</i>	double KO				
4/67.64	<i>Nipal3</i>	<i>Nipal3</i> ^{-/-}	C57BL/6J × 129Sv	No stimulation, SPF conditions	Higher IgE levels and impaired lung functions were observed in males but not in females	Grzmil <i>et al.</i> (2009)
4/67.94	<i>Il28ra</i>	<i>Il28ra</i> ^{-/-}	C57BL/6J	OVA ^S	Higher total IgE levels, augmenting Th2 and Th17 responses, increase in eosinophil and neutrophil infiltration in the BAL fluid	Koltsida <i>et al.</i> (2011)
4/78.17	<i>Tnfrsf8</i>	<i>Tnfrsf8</i> ^{-/-}	C57BL/6	OVA ^S , acute asthma model	Lower OVA-specific IgE, reduced expression of the costimulatory molecule OX40 on CD3 ⁺ T cells	Polte <i>et al.</i> (2009)
5/50.68	<i>Spp1</i> (<i>Opn</i>)	<i>Spp1</i> ^{-/-}	C57BL/6	OVA ^I , SPF conditions	Higher OVA-specific IgE	Kurokawa <i>et al.</i> (2009)

Table 3. Continued

Chr./cM	Tested gene	Genetic modification	Genetic background	Stimulation	Phenotype in comparison with wild type	References
7/8.77	<i>Gpr77</i> (C5L2)	<i>Gpr77</i> -/-	BALB/c	OVA ^S and HDM-induced asthma, SPF conditions	Lower total and specific IgE, eosinophilic airway inflammation, AHR and mucus production, reduced Th2 cytokine production	Zhang <i>et al.</i> (2010)
7/9.93	<i>Rarb</i>	<i>Rarb</i> -/-	C57BL/6J × 129/Sv	No stimulation; SPF conditions (Barton <i>et al.</i> , 2000)	Higher total IgE, dermatitis, inflammatory cell infiltration in organs, myeloid hyperplasia, splenomegaly, defects in cellular and humoral immune responses	Barton <i>et al.</i> (2000) and Weih <i>et al.</i> (1997)
7/45.51	<i>Sema4b</i>	<i>Sema4b</i> -/-	BALB/c C57BL/6	No stimulation or OVA ^S , SPF conditions	Higher total IgE without stimulation, increased OVA-specific IgE response under OVA stimulation	Nakagawa <i>et al.</i> (2011)
7/68.98	<i>Il21r</i>	<i>Il21r</i> -/-	?	No stimulation; stimulation with KLH	Higher total IgE without stimulation; markedly increased total and KLH-specific IgE under KLH stimulation	Ozaki <i>et al.</i> (2002)
8/1.92	<i>Fcer2a</i> (Cd23)	<i>Fcer2a</i> -/-	129/Ola × C57BL/6	OVA ^S , SPF conditions	Higher OVA-specific IgE response, increase of airway eosinophilia and AHR	Haczku <i>et al.</i> (1997)
8/40.26	<i>Il27ra</i> (Wxx1)	<i>Il27ra</i> -/-	C57BL/6	OVA ^S , SPF conditions	Higher serum IgE, augmented immune responses in the cervical lymph nodes and in NALT; reduced local responses of allergic rhinitis, such as sneezes and nasal rubs, and nasal lavage fluid cytokine production	Shinanoe <i>et al.</i> (2009)
8/57.38 9/50.11	<i>Chst4</i> <i>Chst2</i>	<i>Chst2</i> -/- <i>Chst4</i> -/- double KO	C57BL/6	OVA i.n.	Lower OVA-specific IgE, reduced production of IL-4, increase in CD4 ⁺ CD25 ⁺ cell numbers and production of IL-10 in NALT	Ohmichi <i>et al.</i> (2011)
9/2.46	<i>Trpc6</i>	<i>Trpc6</i> -/-	BALB/c	OVA ^S	lower OVA-specific IgE in serum; decrease of IL-5 and IL-13 in the BAL, decrease in airway eosinophilia	Sel <i>et al.</i> (2008)
9/34.22	<i>Smad3</i>	<i>Smad3</i> -/-	?	OVA ^F , SPF conditions	Higher OVA-specific IgE, increased mast cell numbers, reduced thickness of dermis, decrease in the expression of mRNA for IL-6 and IL-1β	Anthoni <i>et al.</i> (2007)
9/71.33	<i>Myd88</i>	<i>Myd88</i> -/-	C57BL/6	Exposure to NO ₂ , OVA ^S	Lower OVA-specific IgE, decreased airway eosinophilia	Bevelander <i>et al.</i> (2007)
10/39.72	<i>Icosl</i>	<i>Icosl</i> -/-	C57BL/6	OVA ^S	Lower OVA-specific IgE; lower lung eosinophilic infiltration, histopathology, mucus production, no AHR	Kadkhoda <i>et al.</i> (2011)

Table 3. Continued

Chr./cM	Tested gene	Genetic modification	Genetic background	Stimulation	Phenotype in comparison with wild type	References
10/74.59	<i>Stat6</i>	<i>Stat6</i> ^{-/-}	BALB/c C57BL/6	OVA ^S , SPF conditions OVA ^S , SPF conditions	No total and specific IgE, no AHR, partially abrogated PE No elevation of total IgE after treatment by OVA, much less AHR, no eosinophilia in BAL	Kuperman <i>et al.</i> (1998) and Akimoto <i>et al.</i> (1998)
10/76.51	<i>Il23a</i>	<i>Il23a</i> knockdown by RNAi	<i>BALB/c</i>	OVA ^S , SPF conditions	Lower total IgE, IL-23, IL-17, and IL-4, dramatically reduced numbers of eosinophils and neutrophils in BAL fluid, reduced inflammation in the lungs	Li <i>et al.</i> (2011)
11/14.36	<i>Rel</i>	<i>Rel</i> ^{-/-}	C57BL/6J × 129/Sv	OVA ^S	No elevation of total IgE, no AHR, no elevation in PE after the treatment by OVA	Donovan <i>et al.</i> (1999)
11/27.75	<i>Ilk</i> (<i>c-Rel</i>)	<i>Ilk</i> ^{-/-}	C57BL/6 C57BL/10	No stimulation, SPF conditions no stimulation, SPF conditions	Higher total IgE in the unimmunised state. Higher total IgE, increased numbers of $\gamma\delta$ T cells	Mueller & August (2003) and Felices <i>et al.</i> (2009)
Nov-32	<i>Il4</i> , <i>Il13</i>	Tg(YAC854G6) Tg(YAC854G6-F1) Tg(YAC131F9) <i>Alox15</i> ^{-/-}	FVB/N	OVA ^S	Higher total IgE, AHR, increased inflammatory cell counts	Symula <i>et al.</i> (1999)
11/42.99	<i>Alox15</i> (12/15-LO)		C57BL/6	OVA ^S	Lower OVA-specific IgE; lower IL-4, IL-13, IFN- γ ; increased lung IgA levels under the airway route of allergen exposure	Hajek <i>et al.</i> (2008)
11/45.25	<i>Trpv1</i>	<i>Trpv1</i> ^{-/-}	C57BL/6	OVA or HDM i.n. sensitisation, SPF conditions No stimulation,	Higher total IgE; higher IL-4 and eosinophils in the BAL fluid under HDM i.n. sensitisation	Mori <i>et al.</i> (2011)
11/45.25	<i>Trpv3</i>	No; natural mutation <i>Trpv3</i> ^{Gly573Ser} transgenic mice	DS-Nh DS	conventional conditions no stimulation; SPF conditions OVA ^S , SPF conditions	Higher total IgE, dermatitis, hairless higher total IgE, dermatitis	Hikita <i>et al.</i> (2002) and Yoshioka <i>et al.</i> (2009)
11/60.95	<i>Thx21</i> (<i>Thet</i>)	<i>Thx21</i> ^{-/-} , T cell-specific conditional expression of T-bet in the thymus, lymph nodes, and spleen	C57BL/6		Higher OVA-specific IgE in the absence of T-bet, and its decrease under restoration of T-bet expression; the duration of T-bet expression correlates with asthmatic phenotype in Dtg/KO mice	Park <i>et al.</i> (2009)

Table 3. Continued

Chr./cM	Tested gene	Genetic modification	Genetic background	Stimulation	Phenotype in comparison with wild type	References
11/60.96	<i>Socs7</i>	<i>Socs7</i> ^{-/-}	129xC57BL/6	No stimulation	Higher total IgE and mast cell infiltration, severe cutaneous disease	Knisz <i>et al.</i> (2009)
11/62.92	<i>Ccr7</i>	<i>Ccr7</i> ^{-/-}	C57BL/6	HDM inhalation, SPF conditions	Higher HDM-specific IgE and greater airway inflammation	Kawakami <i>et al.</i> (2012)
12/8.57	<i>Id2</i>	<i>Id2</i> ^{-/-}	129/Sv	OVA ^S	Higher total IgE, lower OVA-specific IgE, lower eosinophil infiltration in the nasal mucosa, lower local Th2 cytokine transcription than in <i>Id2</i> ^{+/+} mice	Kim <i>et al.</i> (2012)
13/13.19	<i>Agt1a</i>	<i>Agt1a</i> ^{-/-}	C57BL/6	OVA ^S , SPF conditions	Higher OVA-specific IgE; stronger airway inflammation in bronchial tissues; higher numbers of eosinophils and lymphocytes, and higher levels of IL-4, IL-5, IL-13 in BAL fluids	Ohwada <i>et al.</i> (2007)
13/27.68	<i>Nfil3</i>	<i>Nfil3</i> ^{-/-}	C57BL/6	No stimulation, OVA ^S	More than twofold lower IgE in unstimulated state; fivefold lower total IgE, reduced OVA-specific IgE and AHR in response to OVA challenge	Rothman (2010)
13/30.06	<i>Il9</i>	Tg(<i>Il9</i>)	FVB/N	Challenge with <i>Af</i> antigen, conventional conditions	Higher total IgE, AHR, enhanced eosinophilic airway inflammation	McLane <i>et al.</i> , (1998)
14/19.5	<i>Tcrd</i> (<i>Tcrd^{delta}</i>)	<i>Tcrd</i> ^{-/-} ($\gamma\delta$ T-cell KO)	<i>BALB/c</i>	OVA ^S , conventional conditions	Lower OVA-specific IgE, less eosinophilia in BAL fluid, reduced airway inflammation in allergen-induced late airway response	Tamura-Yamashita <i>et al.</i> (2008)
14/24.6	<i>Lgals3</i> (<i>Gal3</i>)	<i>Lgals3</i> ^{-/-}	C57BL/6	OVA ^S	Lower total IgE in serum and BAL fluid, lower eosinophil infiltration, significantly reduced AHR after OVA challenge	Zuberi <i>et al.</i> (2004)
15/40.42	<i>Ppara</i>	<i>Ppara</i> ^{-/-}	129/Sv	No stimulation, tests of 1-year and 2-year-old mice	Higher total IgE in two-, but not in 1-year-old mice; increase in the numbers of splenic plasma cells, development of hepatic inflammatory foci containing mixtures of leucocytes; increase in hepatic levels of TNF- α , IL-6; increase of hepatic IFN- γ only in 2-year-old mice	Qazi <i>et al.</i> (2011)

Table 3. Continued

Chr./cM	Tested gene	Genetic modification	Genetic background	Stimulation	Phenotype in comparison with wild type	References
16/5.81	<i>Socs1</i>	<i>Socs1</i> ^{-/-} <i>Ifng</i> ^{-/-} ; <i>Ifng</i> ^{-/-}	<i>C57BL/6</i>	OVA ^S	Higher specific IgE and eosinophil infiltration in the lungs in double knockouts compared with <i>Ifng</i> ^{-/-} and <i>C57BL/6</i> mice	Lee <i>et al.</i> (2009a)
16/25.72	<i>Cd86</i> , <i>Cd80</i>	<i>Cd80/86</i> ^{-/-} ; <i>Cd80</i> ^{-/-} ; <i>Cd86</i> ^{-/-}	129/SvJae	OVA ^S	No total IgE response, no PE, no AHR in <i>Cd80/86</i> ^{-/-} mice; lower total IgE level, PE, and AHR in <i>Cd80</i> ^{-/-} and <i>Cd86</i> ^{-/-} mice	Mark <i>et al.</i> (2000)
16/26.86						
17/18.59	<i>Tnfr</i>	TNF ^{-/-} (mice deficient in both solTNF and tmTNF) tmTNF knockin mice (exclusively express tmTNF without solTNF)	<i>C57BL/6</i>	OVA ^S , SPF conditions	Reduced lung inflammation, eosinophils and macrophage recruitment in BAL (both in TNF KO and TNF knockin mice), lower OVA-specific IgE in nonmutant BALB/c mice after selective inhibition of solTNF	Maillet <i>et al.</i> (2011)
17/29.08	<i>Ebi3</i>	<i>Ebi3</i> ^{-/-}	<i>BALB/c</i>	OVA ^S i.n., low dose of LPS, SPF conditions	Higher OVA-specific IgE, increased airway inflammation, eosinophilia, increased levels of IL-4, IL-5, and IL-13 in culture supernatants of mediastinal lymph node cells	Dokmeci <i>et al.</i> (2011)
17/29.49	<i>Nrtn</i>	<i>Nrtn</i> ^{-/-}	<i>C57BL/6</i>	OVA ^S , SPF conditions	Higher OVA-specific IgE, eosinophil numbers and IL-4 and IL-5 concentrations in the BAL fluid and lung tissue, enhanced AHR	Michel <i>et al.</i> (2011)
18/2.73	<i>Map3k8</i> (<i>Tpl2</i>)	<i>Map3k8</i> ^{-/-}	<i>C57BL/6</i>	OVA ^S , SPF conditions	Higher total and OVA-specific IgE, more severe bronchoalveolar eosinophilic inflammation	Watford <i>et al.</i> (2010)
18/18.12	<i>Tslp</i>	Tg(TSLP) (inducible, skin-specific)	(<i>C57BL/6</i> × C3H) F ₂ × FVB/N	No stimulation, SPF conditions	Higher total IgE, dermatitis	Yoo <i>et al.</i> (2005)
19/7.4	<i>Gpr44</i> (<i>Crrh2</i>)	<i>Gpr44</i> ^{-/-}	<i>BALB/c</i>	Cry j 1 antigen i.n. repeatedly, SPF conditions	Lower Cry j 1-specific IgE and IgG1 levels, nasal eosinophilia, and IL-4 production by submandibular lymph node cells	Nomiya <i>et al.</i> (2008)
19/13.83	<i>Anxa1</i>	<i>Anxa1</i> ^{-/-}	<i>BALB/c</i>	OVA ^S , SPF conditions	Higher total and OVA-specific IgE	Ng <i>et al.</i> (2011)

Table 3. Continued

Chr./cM	Tested gene	Genetic modification	Genetic background	Stimulation	Phenotype in comparison with wild type	References
X/56.18	<i>Blk</i>	<i>Blk</i> ^{-/-} ; <i>Itk</i> ^{-/-} <i>Blk</i> ^{-/-} double KO	C57BL/6	Passive immunization with murine anti-DNP IgE and consequent DNP-HSA stimulation, SPF conditions	<i>Itk</i> ^{-/-} <i>Blk</i> ^{-/-} double KO mice show highly increased total IgE (higher than WT or single KO), lower serum histamine following Ag challenge, <i>Itk</i> ^{-/-} <i>Blk</i> ^{-/-} skin mast cells have severely decreased granule density	Iyer <i>et al.</i> (2011)

Af, *Aspergillus fumigatus*; Ag, antigen; Ags, antigens; *Agtr1a*, angiotensin II receptor, type 1a; *AHR*, airway hyperresponsiveness; *Alox15* (12/15-LO), arachidonate 15-lipoxygenase; *Anxa1*, annexin A1; *Arnt* (*HIF-1-beta*), aryl hydrocarbon receptor nuclear translocator; *BAL*, bronchoalveolar lavage; *Blk*, Bruton agammaglobulinemia tyrosine kinase; *Carr7*, chemokine (C-C motif) receptor 7; CD3, CD3 antigen; CD4, CD4 antigen; *Cd28*, CD28 antigen; *Cd40*, CD40 antigen; *Cd86*, CD86 antigen; chr., chromosome; *Chst2*, carbohydrate sulfotransferase 2; *Chst4*, carbohydrate (chondroitin 6/keratan) sulfotransferase 4; cM, centiMorgan; *Cmr1*, cannabinoid receptor 1; *Cmr2*, cannabinoid receptor 2; *Ckr* (*Cate*), cathepsin E; Dtg/KO, double transgenic/knockout; *Ebi3*, Epstein-Barr virus induced gene 3; *Fcer1a* (*FcER1*), Fc receptor, IgE, high affinity I, alpha polypeptide; *Fcer2a* (*Cd23*), Fc receptor, IgE, low affinity II, alpha polypeptide; *Fcgr1*, Fc receptor, IgG, high affinity I; *Fcgr2b*, Fc receptor, IgG, low affinity IIb; *Foxp3*, forkhead box P3; *Gata3*, GATA binding protein 3; *Gpr44* (*Crr1b2*), G protein-coupled receptor 44; *Gpr77* (*C5L2*), G protein-coupled receptor 77; HDM, house dust mite; *Icos1*, icos ligand; *Id2*, inhibitor of DNA binding 2; i.n., intranasal; *ifng* (*ifng*), interferon γ (gene); IFN γ interferon γ (protein); IL-1, interleukin 1; *Il1rl1* (*St2*), interleukin-1 receptor-like 1; *Il4*, interleukin 4 (gene); IL-4, interleukin 4 (protein); *Il9*, interleukin 9; IL-10, interleukin 10; *Il13*, interleukin 13; *Il17a*, interleukin 17A; *Il21*, interleukin 21; *Il21r*, interleukin 21 receptor; *Il23a*, interleukin 23, alpha subunit p19; *Il27ra* (*Wsx1*), interleukin 27 receptor, alpha; *Il28ra*, interleukin 28 receptor, alpha; *Infp5d*, inositol polyphosphate-5-phosphatase D; *Itk*, IL2-inducible T-cell kinase; *KLH*, keyhole limpet hemocyanin; KO, knockout; *Lgals3* (*Gal3*), lectin, galactose binding, soluble 3; LPS, lipopolysaccharide; *Lym*, Yamaguchi sarcoma viral (v-yes-1) oncogene homolog; *Map3k8* (*Tpl2*), mitogen-activated protein kinase kinase 8; *Myd88*—myeloid differentiation primary response gene 88; NALT, nasal-associated lymphoid tissue; *Nfya2* (*NEAT1*), nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2; *Nfil3*, nuclear factor, interleukin 3, regulated; *Nipal3*, NIPA-like domain containing 3; *Nr1h*, neurturin; OX40 (Tnfrsf4), OX40 antigen (tumor necrosis factor receptor superfamily, member 4); OVA, ovalbumin; OVA^E, epicutaneous sensitization with ovalbumin; OVA^I, intraperitoneal sensitization with ovalbumin; OVA^S, sensitization and subsequent challenge with ovalbumin; PE, pulmonary eosinophilia; *Phara*, peroxisome proliferator activated receptor alpha; PSA, passive systemic anaphylaxis; *Pigs2* (*Cox-2*), prostaglandin-endoperoxide synthase 2; *Relb*, avian reticuloendotheliosis viral (v-rel) oncogene related B; RNAi, RNA interference (post transcriptional gene silencing); SEA, *Schistosoma mansoni* egg antigen; *Sema4b*, sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain (semaphorin) 4B; *Smad3*, MAD homolog 3 (*Drosophila*); *Sipi*, secretory leukocyte peptidase inhibitor (gene); SLPI, secretory leukocyte peptidase inhibitor (protein); *Socs1*, suppressor of cytokine signaling 1; *Socs7*, suppressor of cytokine signaling 7; solTNF, soluble tumour necrosis factor; SPF, specific pathogen free; *Spp1* (*Opm*), secreted phosphoprotein 1; *Stat6*, signal transducer and activator of transcription 6; *Stat6*, signal transducer and activator of transcription 6; *Thx21* (*Tbet*), T-box 21; *Tcd* (*Tardata*), T-cell receptor delta chain; TD, T cell-dependent; Tg, transgene; TGF- β 1, transforming growth factor beta 1; Th2, T helper 2 cell; TI, T cell-independent; *Tlr2*, toll-like receptor 2; tmTNF, transmembrane tumour necrosis factor; *Tnfrsf8*, tumour necrosis factor receptor superfamily, member 8; *Trpc6*, transient receptor potential cation channel, subfamily V, member 6; *Trpv3*, transient receptor potential cation channel, subfamily V, member 3; *Tsib*, thymic stromal lymphopoietin; WT, wild type.

Names of genes are written in *italics*; names of proteins in regular font.

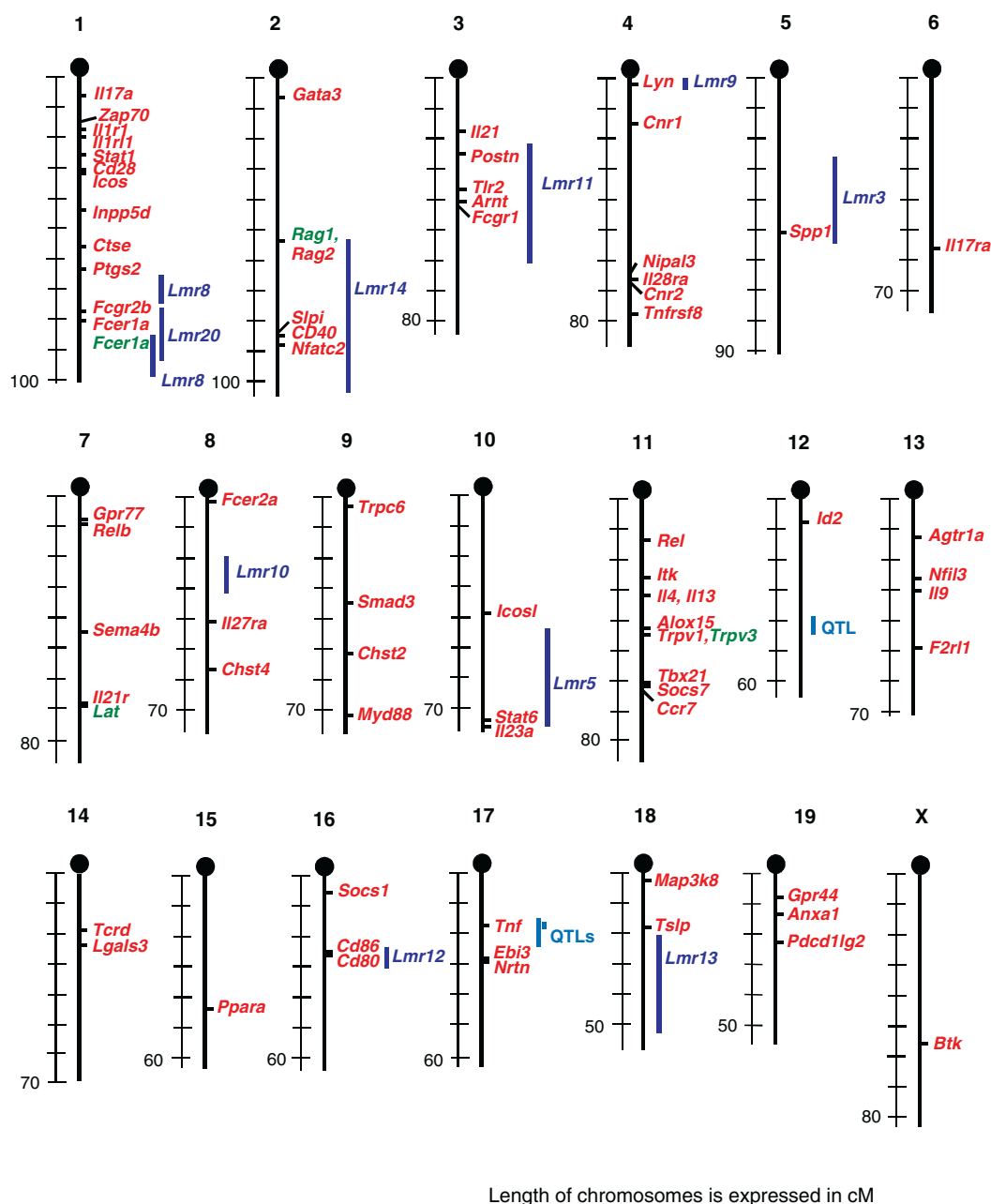


Fig. 1. Figure legend on the next page.

the phenotype is caused by Gly573Ser substitution in the transient receptor potential V3 (*Trpv3*) gene on chromosome 11. The substitution is a gain-of-function mutation which is inherited in autosomal dominant mode and leads to increased ion-channel activity in keratinocytes (Yoshioka *et al.*, 2009) (Table 3).

A range of genes influencing high IgE level associated with dermatitis was identified in experiments with transgenic and knock-out mice (Table 3). The genes of interest were deduced from information on biological pathways and expression data. Mice with knocked-out proteinase cathepsin E (*Ctse/Cate*; chromosome 1) (Tsukuba *et al.*, 2003), thymic

stromal lymphopoietin (*Tslp*; chromosome 18) (Yoo *et al.*, 2005) or the transcription factor avian reticuloendotheliosis viral (v-rel) oncogene-related B (*Relb*; chromosome 7) (Weih *et al.*, 1997; Barton, HogenEsch & Weih, 2000) spontaneously developed high serum IgE levels and dermatitis either in special pathogen-free (SPF) (Weih *et al.*, 1997; Barton *et al.*, 2000; Yoo *et al.*, 2005) or in conventional (Tsukuba *et al.*, 2003) conditions. Prostaglandin-endoperoxide synthase 2 (*Ptgs2/Cox-2*) (chromosome 1) knock-out mice exhibited higher level of specific IgE than wild-type mice in the model of epicutaneous sensitisation with OVA (Laouini *et al.*, 2005).

(c) *Genetics of IgE in mouse models of infectious diseases*

The genetic basis of IgE regulation has been also investigated using mouse models of infectious diseases caused by parasites, which elicit immune responses characterised by elevated IgE production (Table 4) (Fig. 1) (Lipoldová *et al.*, 2000, 2002; Badalová *et al.*, 2002; Menge *et al.*, 2003; Kurey *et al.*, 2009).

The genetics of IgE regulation following gastro-intestinal parasite infection has been studied on a mouse model of nematode disease caused by *Heligmosomoides polygyrus*. The genome-wide search for *H. polygyrus*-controlling genes revealed two IgE-controlling loci on chromosome 12 (39.0–45.0 cM) and on chromosome 17 (15.1–29.4 cM) (Menge *et al.*, 2003) (Table 4). The subsequent genome-wide search in advanced intercross lines confirmed the locus on chromosome 17 and shortened it to 0.7 cM (18.4–19.1 cM) (Behnke *et al.*, 2006) (Table 4) (Fig. 1). These data also led to precise mapping of the previously detected homologous IgE-controlling human locus at 6p21-22 (Daniels *et al.*, 1996; Wjst *et al.*, 1999).

Experiments with knock-out mice revealed an influence of programmed cell death 1 ligand 2 (*Pcd1lg2*)/B7-DC/CD273 (chromosome 19); coagulation factor II (thrombin) receptor-like 1 (*F2rl1*)/protease-activated receptor-2 (*Par2*) (chromosome 13) and interleukin 21 receptor (*Il21r*)

(chromosome 7) on serum IgE level after infection with *Nippostrongylus brasiliensis* (Ishiwata *et al.*, 2010), *Trichinella spiralis* (Park *et al.*, 2011), and *Toxoplasma gondii* (Ozaki *et al.*, 2002), respectively. Interestingly, *PAR2* was associated with serum IgE level in atopic Korean children (Lee *et al.*, 2011). It was also found that interleukin 17 receptor A (*Il17ra*) (chromosome 6) and interleukin 23, alpha subunit p19 (*Il23a*) (chromosome 10) influence total IgE level after infection with *Cryptococcus neoformans* (Szymczak, Sellers & Pirofski, 2012). Silencing of *Il23a* by a small hairpin RNA also dramatically inhibited the OVA-specific IgE responses in a mouse model of asthma (Li *et al.*, 2011).

Mice infected by intracellular parasite *Leishmania major* exhibit a range of susceptibility states depending on the strain of mouse used, where severe infection usually correlates with high serum IgE levels. After *L. major* infection, the susceptible strain BALB/c is a high producer of IgE, and the resistant STS strain is a low producer (Lipoldová *et al.*, 2000). A series of 20 homozygous recombinant congenic (RC) strains, BALB/c-c-STS/Dem (CcS/Dem), which had various IgE responses, was derived from the parental strains. Each CcS/Dem strain contained a different random set of approximately 12.5% genes of the donor strain STS and approximately 87.5% genes of the background strain

Fig. 1. Chromosomal location of mouse genes and loci controlling serum immunoglobulin E (IgE) level. IgE-controlling genes revealed by targeted mutation are shown in red; naturally polymorphic genes influencing IgE level are shown in green. The dark-blue lines represent *Leishmania major* response (*Lmr*) loci harbouring naturally polymorphic genes that control IgE level after *Leishmania major* infection, whereas light-blue lines represent quantitative trait loci (QTLs) without an assigned symbol carrying naturally polymorphic genes controlling IgE level after *Heligmosomoides polygyrus* infection. Positions of genes are given according to Mouse Genome Informatics (<http://www.informatics.jax.org/>). Studies with experimentally induced germ-line mutation or with gene-silencing with RNAi detect genes that are involved in the general regulation of immune reactions leading to IgE production. However, this does not necessarily indicate that natural variation in these genes affects IgE level. Length of chromosomes is expressed in cM. Abbreviations: *Agtr1a*, angiotensin II receptor, type 1a; *Alox15*, arachidonate 15-lipoxygenase; *Anxa1*, annexin A1; *Arnt*, aryl hydrocarbon receptor nuclear translocator; *Btk*, bruton agammaglobulinemia tyrosine kinase; *Ccr7*, chemokine (C-C motif) receptor 7; *Cd28*, CD28 antigen; *Cd40*, CD40 antigen; *Cd80*, CD80 antigen; *Cd86*, CD86 antigen; *Chst2*, carbohydrate sulfotransferase 2; *Chst4*, carbohydrate (chondroitin 6/keratan) sulfotransferase 4; *Cnr1*, cannabinoid receptor 1; *Cnr2*, cannabinoid receptor 2; *Clse*, cathepsin E; *Ebi3*, Epstein-Barr virus induced gene 3; *F2rl1*, coagulation factor II (thrombin) receptor-like 1; *Fcer1a*, Fc receptor, IgE, high affinity I, alpha polypeptide; *Fcer2a*, Fc receptor, IgE, low affinity II, alpha polypeptide; *Fcgr1*, Fc receptor, IgG, high affinity I; *Fcgr2b*, Fc receptor, IgG, low affinity IIb; *Gata3*, GATA binding protein 3; *Gpr44*, G protein-coupled receptor 44; *Gpr77*, G protein-coupled receptor 77; *Icos*, inducible T cell co-stimulator; *Icosl*, icos ligand; *Id2*, inhibitor of DNA binding 2; *Il1r1*, interleukin 1 receptor, type I; *Il1rl*, interleukin-1 receptor-like 1; *Il4*, interleukin 4; *Il9*, interleukin 9; *Il13*, interleukin 13; *Il17a*, interleukin 17A; *Il17ra*, interleukin 17 receptor A; *Il21*, interleukin 21; *Il21r*, interleukin 21 receptor; *Il23a*, interleukin 23, alpha subunit p19; *Il27ra*, interleukin 27 receptor, alpha; *Il28ra*, interleukin 28 receptor, alpha; *Inpp5d*, inositol polyphosphate-5-phosphatase D; *Itk*, IL2-inducible T-cell kinase; *Lat*, linker for activation of T cells; *Lgals3*, lectin, galactose binding, soluble 3; *Lyn*—Yamaguchi sarcoma viral (v-yes-1) oncogene homolog; *Map3k8*, mitogen-activated protein kinase kinase kinase 8; *Myd88*, myeloid differentiation primary response gene 88; *Nfatc2*, nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2; *Nfil3*, nuclear factor, interleukin 3, regulated; *Nipal3*, NIPA-like domain containing 3; *Ntrn*, neuriturin; *Pcd1lg2*, programmed cell death 1 ligand 2; *Postn*, periostin, osteoblast specific factor; *Ppara*, peroxisome proliferator activated receptor alpha; *Ptgs2*, prostaglandin-endoperoxide synthase 2; *Rag1*, recombination activating gene 1; *Rag2*, recombination activating gene 2; *Rel*, reticuloendotheliosis oncogene; *Relb*, avian reticuloendotheliosis viral (v-rel) oncogene related B; *Sema4b*, sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain (semaphorin) 4B; *Smad3*, MAD homolog 3 (drosophila); *Slpi*, secretory leukocyte peptidase inhibitor; *Socs1*, suppressor of cytokine signaling 1; *Socs7*, suppressor of cytokine signaling 7; *Spp1*, secreted phosphoprotein 1; *Stat1*, signal transducer and activator of transcription 1; *Stat6*, signal transducer and activator of transcription 6; *Tbx21*, t-box 21; *Tcrd*—t-cell receptor delta chain; *Tlr2*, toll-like receptor 2; *Tnf*, tumor necrosis factor; *Tnfrsf8*, tumor necrosis factor receptor superfamily, member 8; *Trpc6*, transient receptor potential cation channel, subfamily C, member 6; *Trpv1*, transient receptor potential cation channel, subfamily V, member 1; *Trpv3*, transient receptor potential cation channel, subfamily V, member 3; *Tslp*, thymic stromal lymphopoietin; ζ *ap70*, zeta-chain (TCR) associated protein kinase.

Table 4. Immunoglobulin E (IgE)-controlling loci: mouse models of IgE regulation during parasite infection

Chromosome/ cM	Flanking markers	Locus	Potential candidate gene	Mouse cross	Phenotype	References	Orthologous locus in humans (MGI)	Orthologous locus in humans linked with IgE during allergies in genome-wide studies
1/65.98–75.1	D1Mit42— D1Mit16	<i>Lmr8</i>	<i>Trif54</i> , <i>FasL</i> (Yoshimoto <i>et al.</i> , 1998)	CcS-20 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	1q12-41	1q23-24 (Xu <i>et al.</i> , 2001)
1/84.79–98.03	D1Mit273— D1Mit154	<i>Lmr8</i>	?	CcS-20 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	1q32-42.3	—
1/75.1–95.74	D1Mit16— D1Mit56	<i>Lmr20</i>	<i>Fcer1a</i> , <i>Fcer1g</i> (Lewis <i>et al.</i> , 2004)	CcS-11 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Kurey <i>et al.</i> (2009)	1cen-q12, 1q21-25, 1q31-qter, 2p23.3	1q31.1 (Xu <i>et al.</i> , 2001) 1q23-24 (Xu <i>et al.</i> , 2001)
2/50.23–103.43	D2Mit272— D2Mit74	<i>Lmr14</i>	<i>Trif6</i> (Doi <i>et al.</i> , 2008) <i>Ltk</i> <i>Pla2g</i> <i>Adam33</i>	CcS-16 ↑ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	1p36.33-31, 2p13-q14.1, 2q21.1, 7p14-cen, 11p14.3 -11, 11q11, 15q11-22.2, q26-26.3, 19q13.41, 20pter-qter	7p14.1 (Wjst <i>et al.</i> , 1999; Laitinen <i>et al.</i> , 2001) 7p14.2 (Daniels <i>et al.</i> , 1996; Laitinen <i>et al.</i> , 2004) 11p13 (Dizier <i>et al.</i> , 2000) 15q26.1 (Wjst <i>et al.</i> , 1999) 20q13 (Van Eerdewegh <i>et al.</i> , 2002)
3/21.81–63.4	D3Mit5 —D3Mit125	<i>Lmr11</i>	<i>Il12a</i> (Chehimi & Trinchieri, 1994) <i>Il6ra</i> (Maggi <i>et al.</i> , 1989)	CcS-20 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	1p36.13-q31.3, 3p13-q26.2, 4q22-35, 8q21.2, 12p13.31, 13q12-14.11	4q23 (Laitinen <i>et al.</i> , 2001) 4q35.2 (Wjst <i>et al.</i> , 1999) 3p24.1 (Yokouchi <i>et al.</i> , 2002) 3q24 (Haagerup <i>et al.</i> , 2002)
4/0–4.14	0 - D4Mit264	<i>Lmr9</i>	<i>Lyn</i> (Odum <i>et al.</i> , 2004) <i>Plagl1</i>	CcS-20 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	8q11-13, 8q23-24	8q12 (Gusareva <i>et al.</i> , 2009)
5/30.52–42.62	D5Mit255— D5Mit114	<i>Lmr3</i>	<i>Tsk</i> (Takeba <i>et al.</i> , 2002) <i>Tec</i> (Yang & Olive, 1999)	CcS-5 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Lipoldová <i>et al.</i> (2000); Badalová <i>et al.</i> (2002)	3q25.31, 4p15.1-11, 4q11-13.1	—
5/26.89–55.72	D5Mit54— D5Mit25	<i>Lmr3</i>	<i>Tsk</i> (Takeba <i>et al.</i> , 2002) <i>Tec</i> (Yang & Olive, 1999)	CcS-20 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	1pter-q31.3, 3q25.31, 4p16.3-p11, 4q11-23, 10q22.3, 12q24-24.33, 22cen-q12.3, XYP22.33-22.3, YP11.32-11.3	4q23 (Laitinen <i>et al.</i> , 2001) 12q24.23 (Yokouchi <i>et al.</i> , 2002) 12q22-24.21 (Xu <i>et al.</i> , 2000; Koppelman <i>et al.</i> , 2002)
8/19.01–32.3	D8Mit64— D8Mit8	<i>Lmr10</i>	<i>Msr1</i> <i>Cas3</i>	CcS-20 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	4q21.2, 4q31-35.2, 8p12-11, 8p23.1-21.1, 14q24.1	4q35.2 (Wjst <i>et al.</i> , 1999) 8p23.1 (Dizier <i>et al.</i> , 2000)

Table 4. Continued

Chromosome/ cM	Flanking markers	Locus	Potential candidate gene	Mouse cross	Phenotype	References	Orthologous locus in humans (MGI)	Orthologous locus in humans linked with IgE during allergies in genome-wide studies
10/45.36–70.36	D10Mit161— D10Mit25	<i>Lmr5</i>	<i>Ifng</i> (Coffman & Carty, 1986)	CcS-11 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Kurey <i>et al.</i> (2009)	12cen-q24.1	12q22-24.21 (Xu <i>et al.</i> , 2000; Koppelman <i>et al.</i> , 2002)
10/45.35–77.2	D10Mit67— D10Mit269	<i>Lmr5</i>	<i>Ifng</i> (Coffman & Carty, 1986) <i>Stat6</i> (Shimoda <i>et al.</i> , 1996)	CcS-5 ↓ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Lipoldová <i>et al.</i> (2000) and Badalová <i>et al.</i> (2002)	12cen-q24.1	12q22-24.21 (Xu <i>et al.</i> , 2000; Koppelman <i>et al.</i> , 2002)
10/70.36–76.55	D10Mit35— D10Erd722e	<i>Lmr5</i>	<i>Stat6</i> (Shimoda <i>et al.</i> , 1996)	CcS-16 ↑ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	12q13-q24.1	12q22-24.21 (Xu <i>et al.</i> , 2000; Koppelman <i>et al.</i> , 2002)
12/38.49–44.28	D12Mit177— D12Mit194	?	?	SWR ↑ CBA ↓	IgE induced by <i>Heligmosomoides</i> <i>polygyrus</i> infection	Menge <i>et al.</i> (2003)	14q22.1-31.1, Xq25-26	—
16/24.86–30.83	D16Mit167— D16Mit91	<i>Lmr12</i>	?	CcS-16 ↑ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	3q12-24	3q24 (Haagerup <i>et al.</i> , 2002)
17/14.84–26.71	D17Mit29— D17Mit180	?	?	SWR ↑ CBA ↓	IgE induced by <i>Heligmosomoides</i> <i>polygyrus</i> infection	Menge <i>et al.</i> (2003)	3p24.3, 5q35.3, 6pter-11, 19pter-13.1, 21q22.3	3p24.1 (Yokouchi <i>et al.</i> , 2002) 6p23-21.3 (CSGA, 1997) 6p23-21 (Wjst <i>et al.</i> , 1999) 6p22.2 (Daniels <i>et al.</i> , 1996) 6p24.3 (Haagerup <i>et al.</i> , 2002) 6p23-21.3 (CSGA, 1997) 6p22.3-21.1 (Wjst <i>et al.</i> , 1999)
17/18.4–19.1	D18Mit17— D18Mit46	<i>H2-D</i> <i>Tnf</i>	<i>H2-D</i> <i>Tnf</i> (Sharma <i>et al.</i> , 2006)	SWR ↑ CBA ↓	IgE induced by L4 antigen (against worms)	Behnke <i>et al.</i> (2006)	6p22.1-21	5q23.1-31.1 (Koppelman <i>et al.</i> , 2002)
18/21.09–52.67	D18Mit17— D18Mit46	<i>Lmr13</i>	<i>Csf1r</i> (Sin <i>et al.</i> , 1998) <i>Cd14</i> (Jabara & Vercelli, 1994) <i>Adh2</i> (Kasprowicz <i>et al.</i> , 2000)	CcS-16 ↑ BALB/c ↑	IgE induced by <i>Leishmania major</i> infection	Badalová <i>et al.</i> (2002)	5q21-34, 18p11.3-11, 18q11-22, Xp22.32-22.12	5q23.2 (Haagerup <i>et al.</i> , 2002) 5q33.2 (Yokouchi <i>et al.</i> , 2002) 5q23-33 (Xu <i>et al.</i> , 2000)

↑, high responder; ↓, low responder; ↔, intermediate responder; CcS strains contain a different, random set of approximately 12.5% genes of the 'donor' strain STS and approximately 87.5% genes of 'background' strain BALB/c. IgE-controlling loci were mapped in crosses between relevant recombinant congenic strain and the background strain BALB/c as described in (Lipoldová *et al.*, 2000; Badalová *et al.*, 2002; Kurey *et al.*, 2009), in F₂ hybrids between strains SWR and CBA (Menge *et al.*, 2003), and in advanced intercross lines between strains SWR and CBA (Behnke *et al.*, 2006). Positions of markers and their human orthologues are given according to the Mouse Genome Database (MGI) (<http://www.informatics.jax.org/genes.shtml>, 26 November 2012) corresponding to positions of the flanking markers. *Adam33*, a disintegrin and metalloproteinase domain 33; *Adh2*, adrenergic receptor; beta 2; *Cas3*, caspase 3; *Cd14*, CD14 antigen; *Csf1r*, colony stimulating factor 1 receptor; *Fas*, Fas ligand (TNF superfamily, member 6); *Fcrl4*, Fc receptor, IgE, high affinity I, alpha polypeptide; *Fcrlg*, Fc receptor, IgE, high affinity I, gamma polypeptide; *H2-D*, histocompatibility 2; *Ifng*, interferon gamma; *Il12a*, interleukin 12a; *Il6ra*, interleukin 6 receptor; alpha; L4, fourth-stage larvae; *Lmr*, *Leishmania major* response; *Ltk*, leukocyte tyrosine kinase; *Lyn*, Yamaguchi sarcoma viral (v-yes-1) oncogene homolog; *Msr1*, macrophage scavenger receptor 1; *Plaz2g*, phospholipase A2; *Plgl1*, pleiomorphic adenoma gene 1; *Stat6*, signal transducer and activator of transcription 6, D region; *Tec*, tec protein tyrosine kinase; *Tnf*, tumor necrosis factor; *Tnfrsf4*, tumor necrosis factor (ligand) superfamily, member 4; *Tnfrsf6*, TNF receptor-associated factor 6; *Tsk*, TXK tyrosine kinase.

BALB/c. In this way, the STS genes controlling IgE production became separated among individual CcS/Dem strains. For the genome-wide search for loci controlling serum IgE level, four CcS/Dem strains were used: CcS-5 (the most resistant, the lowest IgE producer), CcS-20 (low IgE producer), CcS-11 (intermediate IgE producer), and CcS-16 (high IgE producer) (Lipoldová *et al.*, 2002). This study revealed 10 IgE-controlling loci and mapped them on chromosome 1 (*Lmr8* and *Lmr20*), chromosome 2 (*Lmr14*), chromosome 3 (*Lmr11*), chromosome 4 (*Lmr9*), chromosome 5 (*Lmr3*), chromosome 8 (*Lmr10*), chromosome 10 (*Lmr5*), chromosome 16 (*Lmr12*) and chromosome 18 (*Lmr13*) (Table 4) (Lipoldová *et al.*, 2000; Badalová *et al.*, 2002; Kurey *et al.*, 2009) (Figs 1 and 2). Some *Lmr* loci had no apparent individual effect, but their influence on IgE level was observed only after interaction with *Lmr* loci on other chromosomes (Badalová *et al.*, 2002) (Fig. 3). It was suggested that in different genetic systems 26–49% of genetic variation can be explained by epistasis (Carlborg & Haley, 2004). The unique feature of RC strains to detect gene interactions with a high efficiency is therefore of great importance (Frankel & Schork, 1996).

From the conserved synteny between mouse and human genomes the orthologous human chromosomal segments were found in the Mouse Genome Database (MGI) (<http://www.informatics.jax.org/genes.shtml>). The segments that were orthologous to *Lmr3*, *Lmr5*, *Lmr8*, *Lmr10*, *Lmr11*, *Lmr12*, *Lmr13* and *Lmr14* in mouse had been already described in genome-wide scans for atopy and asthma loci in humans (Daniels *et al.*, 1996; CSGA, 1997; Wjst *et al.*, 1999; Dizier *et al.*, 2000; Xu *et al.*, 2000, 2001; Laitinen *et al.*, 2001; Haagerup *et al.*, 2002; Howard *et al.*, 2002; Koppelman *et al.*, 2002; Van Eerdewegh *et al.*, 2002; Yokouchi *et al.*, 2002). However, the chromosomal segment identified from orthology with the mouse *Lmr9* has not been found to be linked with IgE levels or any allergic disorder in previous studies in humans. The *Lmr9* locus is a rather precisely mapped to a segment with the most likely length 3.58 Mb and maximal possible length 9.32 Mb on chromosome 4 in the mouse strain CcS-20. The mice homozygous for BALB/c and STS alleles at this locus differed 1.6 times in IgE level (corrected *P* value = 0.00313) (Badalová *et al.*, 2002). The locus in the human region orthologous to *Lmr9*, which is located at a chromosomal segment 8q12, showed suggestive linkage to composite inhalant allergic sensitisation and to nine specific IgEs at the position marked by D8S285 (71 cM) (Gusareva *et al.*, 2009) (Fig. 4). This novel locus of atopy, which was discovered as a result of mouse-to-human integration studies for the first time, contains only a few genes that are good targets for IgE regulation in human.

These observations illustrate the efficiency and power of genome-wide screening in mice in identification of loci/genes of complex traits such as IgE level in humans.

(d) Genetics of IgE in the mouse model of a lymphoproliferative disorder

A gene participating in IgE regulation also has been revealed in a mouse model of a lymphoproliferative disorder. Point

mutations in the gene for adaptor protein linker for activation of T cells (*Lat*) (chromosome 7) prevent it from assembling a signalling complex necessary for the normal development of $\alpha\beta$ T cells or both $\alpha\beta$ and $\gamma\delta$ T cells. Due to this defect, various *Lat* mutants on 129 $\times$ C57BL/6 and 129/SV $\times$ BALB/c backgrounds develop a fatal lymphoproliferative disorder with an overabundance of T cells that chronically produce Th2-type cytokines (e.g. IL-4, IL-5, IL-13). These cytokines, in turn, trigger tissue eosinophilia and massive maturation of plasma cells secreting IgE and IgG1 (Aguado *et al.*, 2002; Sommers *et al.*, 2002; Nunez-Cruz *et al.*, 2003). The effect of the *LAT* gene was also assessed in a study of human patients with allergic asthma from a Chinese population. A significant decrease in mRNA expression of *LAT* gene (16p11.2 locus) was observed in asthma patients in comparison to healthy individuals indicating a possible role of this gene in pathogenesis of allergic asthma (Guo *et al.*, 2008).

(e) IgE regulation during immunodeficiency in mouse

The main causes of Omenn syndrome (OS) are hypomorphic mutations in *RAG* genes (11p13), impairing, but not abolishing, the first steps of V(D)J recombination. Three murine models of the disorder recently have been described, all carrying mutations in *Rag* genes (mouse chromosome 2) (Khiong *et al.*, 2007; Marrella *et al.*, 2007; Gibling *et al.*, 2009). A spontaneous point mutation in the core region of the Rag1 protein, changing an arginine to glutamine at residue 972, resulted in a heritable OS-like phenotype (Khiong *et al.*, 2007). Decreased V(D)J recombination activity in *Rag1*-mutated C57BL/10 mice led to a partial block of T and B cell development and to a high percentage of memory-phenotype T cells. CD4⁺ T cells of the mutant mice expressed unusually high levels of IL-4 and IL-6, which caused elevated IgE levels. Two models were used to study the dilemma of increased IgE levels despite undetectable numbers of B cells in OS: a mouse model generated by the knock-in approach, introducing the hypomorphic mutation R229Q (changing an arginine to glutamine at residue 229) in the Rag2 core domain (Marrella *et al.*, 2007; Cassani *et al.*, 2010) and mice harbouring a homozygous point mutation in which serine 723 of RAG1 is converted to a cysteine (Rag1S723C) (Gibling *et al.*, 2009). It was found that *Rag2*^{R229Q/R229Q} mice have a greater proportion of IgE-secreting cells in secondary lymphoid organs in comparison with wild-type mice (Cassani *et al.*, 2010). Splenic B cells of *Rag1*^{S723C/S723C} mutant mice are skewed towards an early developmental phenotype and preferentially switch to IgE compared with IgG1 (Wesemann *et al.*, 2011) (see also Section II).

Novel models of primary cellular immunodeficiency in mouse were developed by genome-wide N-ethyl-N-nitrosourea (ENU) mutagenesis. The mutant lines were produced from C3HeB/FeJ male mice injected with ENU and then mated with C3HeB/FeJ females. F₁ animals were analysed for dominant mutations by phenotype screening of immunological blood parameters (Jakob *et al.*, 2008). One

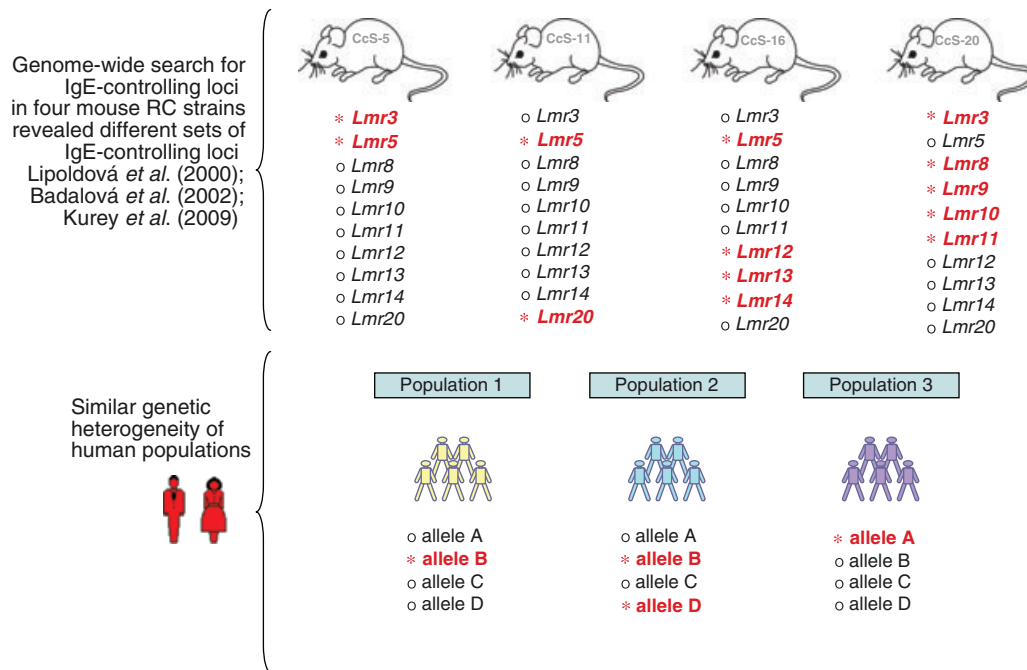


Fig. 2. Recombinant congenic (RC) strains can serve as a model of 'isolated populations' in human linkage disequilibrium studies. Some genes have active alleles (marked as *) only in some populations. Detectability of some alleles can be dependent on epistasis.

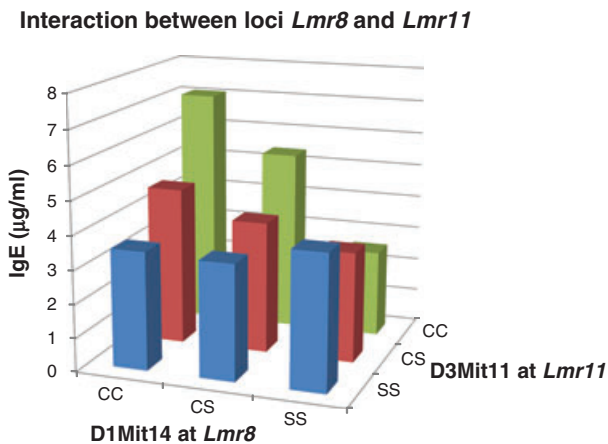


Fig. 3. Control of serum immunoglobulin E (IgE) level in mouse by mutual gene interactions of alleles of two loci, *Lmr8* and *Lmr11*. C and S indicates the presence of BALB/c and STS allele, respectively. CC, BALB/c homozygotes; SS, STS homozygotes; CS, heterozygotes.

of the resulting mouse mutants, designated $\Delta T3$, displayed a combined phenotype of increased IgE levels, absence of peripheral T cells, block in late thymocyte differentiation and an abrogated specific humoral immune response. Chromosomal mapping and sequencing of candidate genes revealed a novel point mutation in the kinase domain of the TCR ζ chain-associated protein kinase (*Zap70*) (chromosome 1) responsible for increased IgE level in mutant mice with a recessive pattern of inheritance. *Zap70* plays a crucial role in TCR signalling (Chan *et al.*, 1992), T-cell activation,

thymocyte development, NK activation, and NK T-cell development (Hivroz, 2005). However, the exact mechanism leading to the increase of IgE level in mutant mice remains unclear (Jakob *et al.*, 2008).

(3) Sex-related differences in genetic regulation of IgE in human and mouse

Sexual dimorphism in total serum IgE and allergen (antigen)-specific IgE levels often has been shown in human studies. In different general population samples, total IgE level was higher in males than in females (Barbee *et al.*, 1981; Lynch *et al.*, 1982; Grigoreas *et al.*, 1993; Kerkhof *et al.*, 1996; Johnson, Peterson & Ownby, 1998). The level of total and specific IgE was significantly higher in males than in females during an outbreak of American cutaneous leishmaniasis in Venezuela (Lynch *et al.*, 1982). The level of specific IgE to dust mite (*Dermatophagoides pteronyssinus*) was significantly higher in males, and at the same time birch-specific IgE was lower in males than in females (Kerkhof *et al.*, 1996). In 4-year-old children, cat-specific IgE was considerably more prevalent in girls, but specific IgE to ragweed allergens was higher in boys (Johnson *et al.*, 1998).

In genetic studies, distinct IgE regulation among males and females was also demonstrated. Sex-stratified genome-wide linkage analysis in extended pedigrees with asthma from Costa Rica revealed a novel male-specific locus influencing total IgE on chromosome 20p12, where three SNPs in jagged 1 protein (*JAG1*) and ankyrin repeat domain 5 (*ANKRD5*) showed association with total IgE (Raby *et al.*, 2007). Later in the same population a female-specific locus 5q21-32 for IgE to German cockroach (*Blattella germanica*) was identified

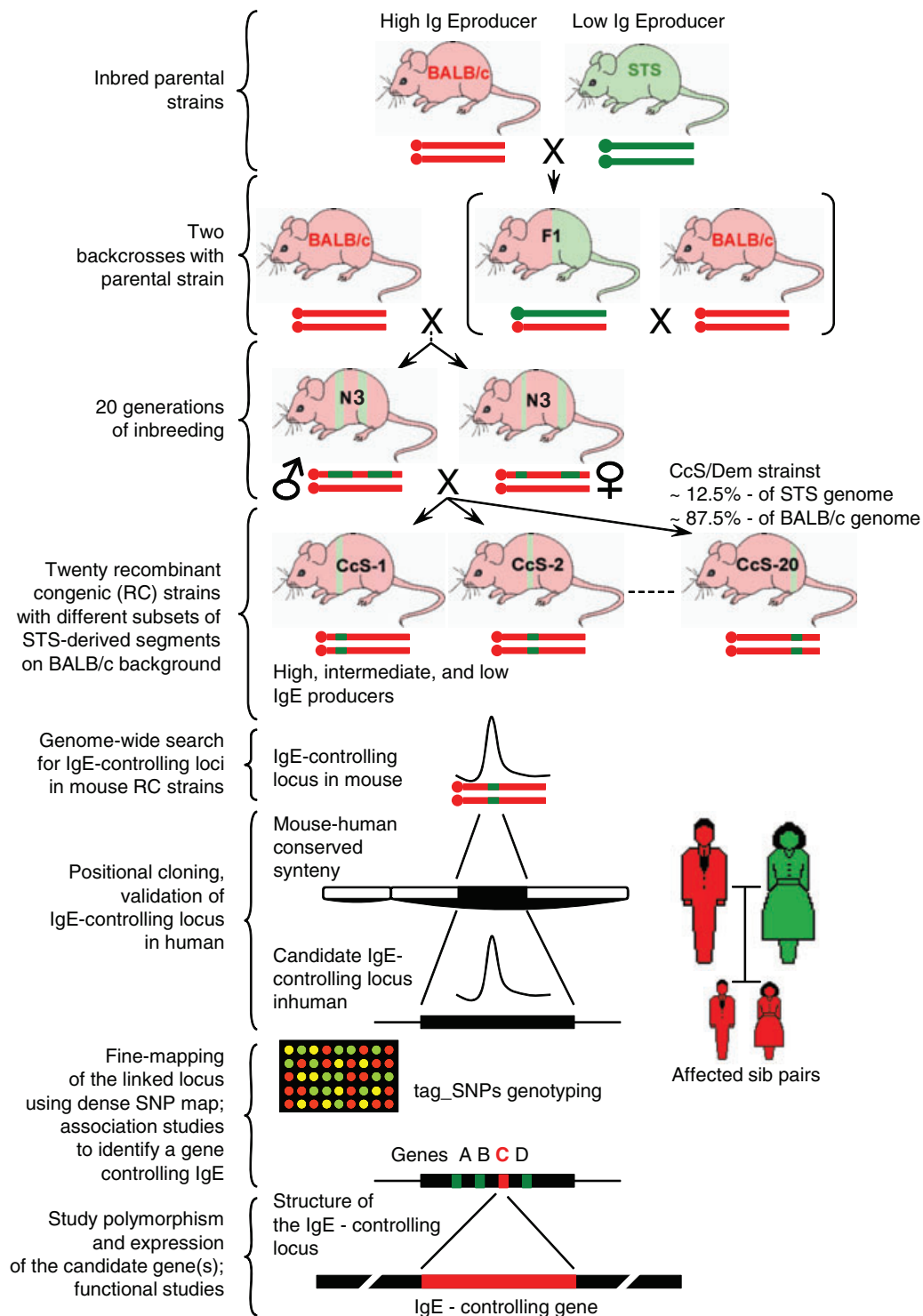


Fig. 4. Combination of genome-wide scan for immunoglobulin E (IgE)-controlling loci in mice and the candidate gene approach in humans. The mouse breeding scheme is shown that was used to generate the recombinant congenic (RC) strains CcS/Dem developed for genome-wide search of IgE-controlling loci in mouse (Demant & Hart, 1986). Extrapolation of mouse IgE-controlling loci to human was carried out using conserved synteny between mouse and human genomes. Final validation of the IgE-controlling locus in humans used a positional cloning approach, fine-mapping of the locus and functional analysis. SNP, single nucleotide polymorphism.

(Hunninghake *et al.*, 2008). Polymorphism in the cytotoxic T-lymphocyte-associated protein 4 gene (*CTLA4*, at locus 2q33) was associated with total IgE in atopic females from Taiwan (Yang *et al.*, 2004) and cysteinyl leukotriene receptor 1 gene (*CYSLTR1*, locus Xq13.2-q21.1) was associated with atopy composite phenotype (high total IgE and sensitisation to at least one inhalant allergen) in females from white British families (Duroudier *et al.*, 2009). The ATA haplotype in *IL10* gene promoter was associated with high IgE level only in males from a Finish population (Karjalainen *et al.*, 2003).

In mice, sexual dimorphism was observed in pulmonary allergic response, where female BALB/c mice developed significantly higher IgE level to OVA challenges than male mice (Corteling & Trifilieff, 2004; Melgert *et al.*, 2005). In model of allergic rhinitis, CBA/J mice were repeatedly intranasally sensitised with phospholipase A₂ (PLA₂), a major bee (*Apis mellifera*) venom antigen. Females produced significantly higher specific IgE to PLA₂ than males, and castrated male mice produced significantly higher PLA₂-specific IgE than control male mice. The level of PLA₂-specific IgE was decreased by treatment of castrated male mice with testosterone (Yamatomo *et al.*, 2001).

V. CONCLUSIONS

(1) Mammalian IgE and IgG have evolved through gene duplication and subsequent evolution of IgY. In this duplication and evolution the anaphylactic and opsonic activities of IgY were separated between IgE and IgG, respectively. Anaphylactic reaction has life-threatening side effects and its separation to a distinct molecule allowed its specific downregulation.

(2) IgE plays a crucial role in defence against helminths and other parasitic infections, in development of allergic reactions, in some anti-tumour defences and in several autoimmune diseases. Its level is also increased in several immunodeficiencies.

(3) The level of IgE is dependent on environmental stimuli and on genetic factors. The mode of the genetic regulation of IgE seems to be different in various pathological states. In allergic and infectious diseases, IgE is likely to be influenced by multiple interacting genes, whereas IgE level in immunodeficiencies depends on mutations in single genes inherited in a dominant or recessive manner.

(4) Remarkably, despite various study designs in humans and in mouse models, IgE-controlling loci/genes in different diseases are often the same in the two species. This provides many new insights into the development of susceptibility to complex diseases concomitant with elevated IgE levels. These observations indicate at least partially similar etiology for many complex diseases that involve an IgE-dependent immune response. Therefore, the study of genetic regulation of IgE in one pathological state can give clues to understanding the others.

VI. ACKNOWLEDGEMENTS

We thank Dr. Rosemary W. Elliott and Dr. Peter Demant from the Department of Molecular and Cellular Biology of the Roswell Park Cancer Institute in Buffalo, New York, USA for careful reading of the manuscript. This work was supported by the Academy of Sciences of the Czech Republic (Project Grant Nr. RVO 68378050), by the Grant Agency of the Czech Republic (Grant GACR 310/08/1697), and by the Ministry of Education of the Czech Republic (Grant LH12049). The PhD study of I.K. was partly supported by the third Faculty of Medicine, Charles University in Prague, Czech Republic.

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(Received 7 July 2012; revised 14 June 2013; accepted 31 July 2013)