

Genetic variability of the high-affinity IgE receptor α -subunit (Fc ϵ RI α)

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Abstract Our knowledge on the variability of *FCERIA* gene encoding for α -subunit of the high-affinity immunoglobulin E receptor (Fc ϵ RI) that plays a central role in the pathogenesis of allergy and related disorders, has been recently much extended. Last findings from *FCERIA* mutational screening and genetic association studies, followed by functional analyses of the polymorphisms, are briefly summarized in this mini-review. The association between *FCERIA* gene variants and total serum IgE levels seems especially interesting and, supported by functional analyses of polymorphisms, may provide a rationale for pharmacogenetic studies on anti-IgE therapy that indirectly suppresses Fc ϵ RI expression.

Keywords *FCERIA* · Fc ϵ RI · Fc ϵ RI α · (Genetic) polymorphism · IgE · IgE receptor

The high-affinity immunoglobulin E (IgE) receptor (Fc ϵ RI) plays a key role in the pathogenesis of allergy and related disorders [1–3]. The receptor is expressed on human mast cells and basophils, and is composed of three different subunits that form $\alpha\beta\gamma_2$ heterotetramer [1–3]. Some other human cells, such as monocytes, Langerhans cells, dendritic cells and eosinophils also can express Fc ϵ RI, but on these cells it is composed of only two subunits forming $\alpha\gamma_2$ heterotrimer [1–3].

Although our knowledge on the structure and function of the *FCERIA* gene, encoding for Fc ϵ RI α -chain (Fc ϵ RI α), was recently much broadened [4–9], genetic studies on its variability in human were very few [2]. Thus, until 2003 only two reports were published

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[10, 11], which was even more surprising in contrast to a huge number of studies on variability of the *FCER1B* (*MS4A2*) gene encoding for FcεRI β-subunit (FcεRIβ), conducted since early 90s [2].

Very recently, several novel studies reported on unusual genetic variability of *FCERIA* and its relationship to atopy measures or allergic disorders in human [12–24]. The gene, though conserved in its coding region, shares some common 5'-untranslated region variants across several human populations. Current knowledge on human *FCERIA* genetic variability is concisely summarized below.

Mutational screening studies

Initially, human *FCERIA* gene was thought to be composed of 5 exons regulated by a single promoter [25–27]. It turned out later, that two additional untranslated exons (1A, 2A) and a distal regulatory region are localized upstream of those originally described [5, 8, 9]. Novel regulatory region was called a “distal” promoter, whereas the other one preceding coding exons was renamed to a “proximal” [8, 9].

Mutational screening in American Caucasians and African Americans showed no mutation in exons 1–5, whereas three single nucleotide polymorphisms (SNPs) were found in proximal promoter [10]. One of them, –335 C>T (–344 C>T¹), was reported to be frequent in both ethnic groups, while two other mutations: –770 A>C (–778 A>C*) and –664 G>A (–673 G>A*) were shown to be quite frequent in African Americans and very rare in American Caucasians [10]. A rarity of the latter two mutations (–778 A>C and –673 G>A) was also observed in Polish Caucasians [23], while none of them was found in Korean [15] and Japanese [23] East Asians. Another investigators reported on the proximal promoter SNP –66 T>C (–95 T>C*) discovered in Japanese East Asians [11]. Recently, however, two independent research groups demonstrated co-presence of both –344 C>T and –95 T>C SNPs in Polish Caucasians [12, 13] and Korean East Asians [14, 15]. A highly conservative sequence of exons 1-5 in Korean East Asians [16] and Polish Caucasians [17] confirmed the original American report [10]. Only one sporadic missense but semiconservative (T62S) mutation within exon 3 (+1671 A>T) was described in a Polish allergic subject [17].

The novel *FCERIA* regions (exons 1A and 2A, distal promoter) were also very recently screened for mutations [15, 16, 18–20]. The distal promoter region was shown to be again highly conserved in Korean East Asians [15] and Polish Caucasians [19]. No mutations were found in exon 2A in Poles [18] and Koreans [16]. Only a one rare –12663 A>G polymorphism was detected upstream close to exon 2A in Polish subjects [18]. On the contrary, two frequent polymorphisms, –18674–18675 AA ins>del and –18483 A>C, were found in exon 1A in Polish Caucasians [19] and Japanese East Asians [20].

FCERIA mutational screening studies are summarized in Table 1 and the sequence of the genetic variants is summarized in Table 2.

¹ *All *FCERIA* polymorphisms denoted by “asterisk” in the current paper are numbered according to translation start site; –778 A>C, –673 G>A and –344 C>T were originally described as –770 A>C, –664 G>A and –335 C>T, respectively [10]; in papers by Hasegawa et al. [11] and Kanada et al. [22], –95 T>C and –344 C>T polymorphisms were numbered according to transcription start site as –66 T>C and –315 C>T, respectively.

Table 1 Mutational screening studies on *FCERIA* gene

<i>FCERIA</i> gene region (-s)	Screened population ethnicity (-ies)	Finding (-s)	Reference (-s)
Proximal promoter, exons 1–5	American Caucasians and African Americans	Three SNPs (–770 A>C ^a , –664 G>A ^a and –335 C>T ^b) in proximal promoter, conservation of exons 1–5	Shikanai et al. (2002) [10]
Proximal promoter, exon 1	Japanese East Asians	One SNP (–66 T>C ^a) in proximal promoter, conservation of exon 1	Hasegawa et al. (2003) [11]
Proximal promoter	Polish Caucasians	Two SNPs in proximal promoter (–344 C>T and –95 T>C)	Potaczek et al. (2006) [12], Sanak et al. (2007) [13]
Proximal promoter, distal promoter	Korean East Asians	Two SNPs in proximal promoter (–344 C>T and –95 T>C), conservation of distal promoter	Kim et al. (2006) [14], Bae et al. (2007) [15]
Exon 2A	Polish Caucasians	One SNP near upstream of exon 2A (–12663 A>G), conservation of exon 2A	Potaczek et al. (2006) [18]
Distal promoter, exon 1A	Polish Caucasians	Two polymorphisms in exon 1A (–18674–18675 AA ins>del, –18483 A>C), conservation of distal promoter	Potaczek et al. (2007) [19]
Exon 2A, exons 1–5	Korean East Asians	Conservation of exon 2A and exons 1–5	Kim et al. (2007) [16]
Exons 1–5	Polish Caucasians	Conservation of exons 1–5, one accidental (1/432 chromosomes) mutation (+1671 A>T) in exon 3	Potaczek et al. (2007) [17]
Exon 1A	Japanese East Asians	Two polymorphisms in exon 1A (–18674–18675 AA ins>del, –18483 A>C)	Potaczek et al. (2008) [20]
Proximal promoter	Polish Caucasians, (Japanese East Asians)	–778 A>C and –673 G>A present in proximal promoter upstream of –344 C>T in Polish Caucasians (but not in Japanese East Asians)	Potaczek et al. (2008) [23]

FCERIA, the gene encoding for the α -chain of the high-affinity immunoglobulin E receptor (Fc ϵ RI α); SNP, single nucleotide polymorphism

^a Numbering according to translation start site: –770 A>C → –778 A>C, –664 G>A → –673 G>A, –335 C>T → –344 C>T, –66 T>C → –95 T>C

Genetic association studies on *FCERIA* gene

None of three *FCERIA* proximal promoter SNPs –673 G>A, –778 A>C or –344 C>T was associated with asthma in African Americans or American Caucasians [10]. Another proximal promoter SNP, –95 T>C, was associated with atopic dermatitis (AD) in Japanese population [11]. Significant fraction of non-allergic individuals was found to carry the heterozygous –95 TC genotype, whereas most of patients suffering from AD were the homozygotes for –95 TT genotype [11]. *FCERIA* proximal promoter SNPs: –344 C>T and –95 T>C, were reported to associate with aspirin-induced chronic urticaria (AICU) in Koreans [14, 15]. Higher frequencies of –344 T allele and –344 CT/TT genotype were observed in patients with AICU when compared to subjects having aspirin-tolerant chronic urticaria (ATCU) or controls. In addition, –95 C allele and –95 TC genotype of the other SNP were also found to be more frequent in subjects with AICU when compared to ATCU

Table 2 Genomic localization of *FCERIA* mutations reported so far

Mutation number (according to translation start site)		Mutation within its genomic surrounding
–18674–18675 AA ins>del ^a (rs10557633) ^b	AA (insertion)	aatccagttctctctaataatcAAagagagcctcaaattgttgctatgttc
		or ^a
		aatccagttctctctaataatcAAagagagcctcaaattgttgctatgttc
	-- (deletion)	aatccagttctctctaataatcagagagcctcaaattgttgctatgttc
		or ^a
		aatccagttctctctaataatcagagagcctcaaattgttgctatgttc
–18483 A>C (rs2494262)	A	agatcatccttttgagaattcctAcatgctactaagaggtaaggaaggta
	C	agatcatccttttgagaattcctCcatgctactaagaggtaaggaaggta
–12663 A>G	A	caatttaattttatctctgttctAaaattcttttcagtctccagcatcct
	G	caatttaattttatctctgttctGaaattcttttcagtctccagcatcct
–778 A>C ^c (rs16841988)	A	ggcacagtagagaaaggaggtctctgaAaatgtttccaatttcgctggt
	C	ggcacagtagagaaaggaggtctctgaCaatgtttccaatttcgctggt
–673 G>A ^c	G	gcaggaaatfaacaagaaaagcGttgtagctctggtgaatcccaaaag
	A	gcaggaaatfaacaagaaaagcAttgtagctctggtgaatcccaaaag
–344 C>T ^{c,d} (rs2427827, rs60829060)	C	agttgctgctgttttattctgcCctcccttgcatcccaacttttctaagtt
	T	agttgctgctgttttattctgcTctcccttgcatcccaacttttctaagtt
–95 T>C ^d (rs2251746, rs61256669)	T	tgatgggftaaccagatatgaTcacagaaaacatttccttctgttttgg
	C	tgatgggftaaccagatatgaCacagaaaacatttccttctgttttgg
+1671 A>T (T62S)	A	ggaacaatttcttgaagtcagttccAccaatggttcacaaatggcagc
	T	ggaacaatttcttgaagtcagttccTccaatggttcacaaatggcagc

FCERIA, the gene encoding for the α -chain of the high-affinity immunoglobulin E receptor (Fc ϵ RI α)

^a This mutation could be also numbered as –18673–18674 AA ins>del

^b All rs numbers are taken from NCBI dbSNP system (<http://www.ncbi.nlm.nih.gov/projects/SNP/>)

^c –778 A>C, –673 G>A and –344 C>T mutations were originally described as –770 A>C, –664 G>A and –335 C>T, respectively [10]

^d In papers by Hasegawa et al. [11] and Kanada et al. [22], –95 T>C and –344 C>T polymorphisms were numbered according to transcription start site as –66 T>C and –315 C>T, respectively

[14, 15]. This association with aspirin hypersensitivity failed, however, to replicate in Polish subjects [12, 13] but inconsistent results could be explained by a different selection criteria for the Polish group, which included subjects both with asthma and urticaria, and by ethnic differences in SNPs frequencies between Polish Caucasians and Korean East Asians [12–15]. Very recently, a lack of association between –344 C>T or –95 T>C SNP and asthma, irrespective of aspirin hypersensitivity, was reported in Koreans [24].

Several studies described a consistent genetic association between *FCERIA* variants, -344 C>T and -18483 A>C , and total serum IgE levels in allergic subjects [10, 12, 13, 15, 19, 21]. The proximal promoter variant -344 C>T , being discovered first, was studied more extensively. In brief, -344 T allele or -344 TT genotype was observed to be directly or indirectly (reported as protective -344 CC genotype) related to the higher total serum IgE levels [10, 12, 13, 15, 19, 21]. Particularly, in American asthmatics of Caucasian ethnicity, -344 CC homozygotes were more frequent among subjects having lower total serum IgE levels [10]. This indirect association was later confirmed by two independent groups [12, 13, 15, 19]. The Polish Caucasian allergic patients homozygous for -344 TT genotype had higher total serum IgE levels when compared to subjects carrying -344 C allele [12, 13, 19]. The Korean patients suffering from AICU and carrying -344 T allele had elevated total serum IgE levels, when compared to the homozygotes -344 CC [15]. A statistical trend toward association with higher total serum IgE levels was also observed in Polish allergic subjects with *FCERIA* -18483 CC genotype [19]. This association was significant when the analysis was conducted in a subgroup of asthmatics [19]. Of interest, it was also demonstrated that *FCERIA* -344 C>T – 18483 A>C diplotypes are associated with total serum IgE levels in allergic subjects along with the variant of the gene for β -subunit of the receptor, *FCERIB* -109 T>C , in additive but not multiplicative manner [21]. Highest serum IgE concentrations were observed in allergic subjects with *FCERIA* -344 TT – 18483 CC & *FCERIB* -109 TT combined genotype, whereas the lowest levels were found in those with *FCERIA* -344 CT/CC – 18483 AC/AA & *FCERIB* -109 TC/CC genotype group [21], which further expanded the previous studies on *FCERIB* -109 T>C genetic variant [28, 29]. One study, conducted in Korean asthmatics with or without aspirin hypersensitivity, failed to replicate association between -344 C>T genetic variant and total serum IgE levels [24].

Autoimmune background of allergic diseases was widely investigated [30–32]. Specifically, the presence of autoantibodies against IgE and/or $\text{Fc}\epsilon\text{RI}\alpha$ in allergic disorders, mainly chronic idiopathic urticaria [30, 31] but also asthma [32], was commonly found. Thus, not surprisingly, *FCERIA* proximal promoter polymorphisms were also tested for association with these autoimmune phenomena [12, 15]. Neither -344 C>T nor -95 T>C variants within the proximal promoter were associated with the presence of autoantibodies against IgE and/or $\text{Fc}\epsilon\text{RI}\alpha$, as screened for by autologous serum skin test (ASST) or histamine release test (HRT), in a heterogeneous group of allergic subjects with either asthma or urticaria [12]. In addition, none of these two SNPs associated with the presence of common markers for autoimmunity as antithyroglobulin, antimicrosomal or antinuclear autoantibodies in patients suffering from AICU [15].

Specific IgE antibodies against staphylococcal enterotoxins were recently implicated in the pathogenesis of several allergic disorders, for example atopic dermatitis, nasal polypsis or aspirin-induced asthma [33–35]. Consequently, the association between *FCERIB* -109 T>C polymorphism and specific IgE against staphylococcal enterotoxin B (IgE-SEB) or A (IgE-SEA) in subjects with aspirin-intolerant asthma (AIA) was reported [36]. The prevalence of IgE-SEB and IgE-SEA antibodies was higher in subjects with *FCERIB* -109 TT genotype [36], the one associated with higher total serum IgE levels in allergic subjects [21, 28, 29]. Similar observations were reported for *FCERIA* -344 C>T SNP [12]. *FCERIA*– 344 TT genotype, also associated with higher total serum IgE levels, correlated with a higher prevalence of IgE-SEB in a mixed group of allergic subjects [12]. An association between -344 T allele carrying status and higher prevalence of IgE-SEA antibodies was also observed in subjects with aspirin-intolerant asthma [24]. In the same group

of patients, also –95 C>T polymorphism was associated with the prevalence of IgE-SEA and specific IgE against toxic shock syndrome toxin 1 (TSST-1) antibodies [24].

A summary of *FCER1A* genetic association studies is given in Table 3.

Table 3 Association studies on *FCER1A* gene variants

Findings of the study	Population ethnicity	Reference (-s)
Homozygosity for the C variant at locus –344 more common in Caucasian (but not African American) asthmatic patients with total serum IgE levels in the lower quartile than in the upper quartile. None of –778 A>C, –673 G>A and –344 C>T polymorphisms associated with asthma.	African Americans, American Caucasians	Shikanai et al. (2002) [10]
Significant portion of non-allergic individuals with heterozygous –95 TC ^a genotype and most of patients suffering from AD with homozygous –95 TT genotype.	Japanese East Asians	Hasegawa et al. (2003) [11]
Higher total serum IgE levels in allergic subjects with –344 TT genotype. Neither –344 C>T nor –95 T>C polymorphism associated with the presence autoantibodies against IgE/FcεRI ^b or with aspirin hypersensitivity. A correlation between IgE-SEB positivity and –344 C>T genotype.	Polish Caucasians	Potaczek et al. (2006) [12], Sanak et al. (2007) [13]
Higher frequency of the –344 T allele and –344 CT/TT genotype in the patients with AICU when compared to subjects ATCU or to controls. Higher frequency of the –95 C allele and –344 TC genotype in subjects with AICU compared to ATCU. Elevated concentrations of total serum IgE levels and a higher rate of atopy in the patients with AICU carrying –344 T allele. Neither –344 C>T nor –95 T>C polymorphism associated with the presence of antithyroglobulin, antimicrosomal or antinuclear autoantibodies in subjects with AICU.	Korean East Asians	Kim et al. (2006) [14], Bae et al. (2007) [15]
Higher total serum IgE levels in allergic subjects with –344 TT genotype. Elevated total serum IgE concentrations in asthmatics homozygous for rare allele of either –344 C>T or –18483 A>C polymorphisms.	Polish Caucasians	Potaczek et al. (2007) [19]
Additive but not multiplicative association of –344 C>T and –18483 A>C <i>FCER1A</i> polymorphisms and –109 T>C <i>FCER1B</i> gene variant with total serum IgE levels in allergic patients: the highest IgE concentrations present in subjects with –344 TT–18483 CC <i>FCER1A</i> diplotype and –109 TT <i>FCER1B</i> genotype.	Polish Caucasians	Potaczek et al. (2007) [21]
Neither –344 C>T nor –95 T>C polymorphism associated with asthma or total serum IgE levels, irrespective of aspirin hypersensitivity. <i>FCER1A</i> variants associated with specific IgE antibodies against staphylococcal enterotoxins in subjects with aspirin-intolerant asthma (–344 C>T, IgE-SEA; –95 T>C, IgE-SEA, IgE-TSST-1).	Korean East Asians	Palikhe et al. (2008) [24]

FCER1A, the gene encoding for the α -chain of the high-affinity immunoglobulin E receptor (FcεRI α); AD, atopic dermatitis; FcεRI, the high-affinity immunoglobulin E receptor; IgE-SEB, specific IgE against staphylococcal enterotoxin B; AICU, aspirin-induced chronic urticaria; ATCU, aspirin-tolerant chronic urticaria; *FCER1B*, the gene encoding for the β -chain of the high-affinity immunoglobulin E receptor (FcεRI β); IgE-SEA, specific IgE against staphylococcal enterotoxin A; IgE-TSST-1, specific IgE against toxic shock syndrome toxin 1

^a In paper by Hasegawa et al. [11], –95 T>C polymorphism was numbered according to transcription start site as –66 T>C

^b Ascertained by autologous serum skin test (ASST) and histamine release test (HRT)

Functional studies

Our knowledge on regulation of human *FCERIA* gene expression extended much during the last decade [4–9]. In brief, *FCERIA* transcription is controlled in a cell-specific manner by two regulatory regions, proximal and distal promoters [4–9]. Mast cell-specific regulatory mechanism of *FCERIA* constitutive expression involves a transactivation by PU.1, GATA-1 and YY-1 transcription factors and transrepression by Elf-1, binding to the proximal promoter [4–9, 37]. The other regulatory region, distal promoter, is responsible for inducible expression of the gene in the presence of interleukin-4 (IL-4) [8, 9]. Distal promoter is negatively affected by PU.1, YY-1 and Elf-1, whereas positive regulator has not been identified so far [8, 9]. Details on *FCERIA* transcriptional regulation could be found elsewhere [4–9, 37].

Two out of three *FCERIA* polymorphisms, for which genetic associations were observed using clinical and/or biochemical correlations [10–15, 19, 21], were tested for their functional effects [11, 14, 15, 22]. Firstly, it was demonstrated that in the presence of –95 T allele (–66* in the promoter numbering) in *FCERIA* proximal promoter, a supernumerary binding motif for GATA-1 transcription factor is created, resulting in the overlapping double GATA-1 elements [11]. This, in turn, amplifies activity of –95 T variant proximal promoter in mast cell and basophil cell lines, via a higher affinity for binding of GATA-1 when compared to that with –95 C variant [11]. A confirmation of this molecular mechanism is a decrease in FcεRI surface expression on peripheral blood basophils, in subjects carrying –95 C allele [11]. Multiple linear regression analysis in this study succeeded to demonstrate that this SNP actually relates with FcεRI expression level in an IgE level-independent manner [9, 11]. Secondly, two other studies demonstrated functional activity of the other common proximal promoter SNP, –344 C>T [14, 15, 22]. The presence –344 T allele in *FCERIA* proximal promoter sequence was shown to result in higher transcriptional activity when compared to –344 C variant [14, 15]. Lower activity of –344 C variant was suggested to result from preferential binding of Myc-associated zinc finger protein (MAZ) transcription factor [15]. Moreover, IgE-mediated histamine release from basophils ascertained in AICU subjects carrying –344 T variant was higher when compared to those homozygous for –344 CC [15]. In the other study [22], while also demonstrating the higher activity of –344 T (–315* in the promoter numbering) variant proximal promoter in mast cell and basophil cell lines, an additive effect of both frequent SNPs, –344 C>T and –95 T>C, on transcriptional activity of proximal promoter was shown [22]. However, in this study [22] different transcription factors were identified, as related to –344 C>T variant's regulation on the proximal promoter activity. In brief, a common transcription factor Sp1, but not MAZ, recognizes –344 C variant specifically, whereas other transcription factors of high-mobility group 1 and/or 2 bind to the stronger promoter –344 T variant [22]. Moreover, surface expression of FcεRI immunoreactivity on basophils from peripheral blood of –344 TT homozygotes or –344 T variant carriers was both higher when compared to –344 CC homozygotes [22].

Functional studies are shortly summarized in Table 4.

It is well documented that in the presence of IgE expression of cell surface FcεRI increases [1–3]. However, –344 T variant or –344 TT genotype was associated with higher total serum IgE levels in allergic subjects [10, 12, 13, 15, 19]. Moreover the proximal promoter of *FCERIA* carrying –344 T variant was shown to have higher transcriptional activity [14, 15, 22]. Thus, a mechanism by which –344 C>T SNP might affect serum IgE in allergic subjects, considering its impact on FcεRI expression, is still elusive. A tempting possibility could be SNP-dependent variability of the receptor on antigen

Table 4 Functional studies on *FCERIA* gene polymorphism

Findings of the study	Reference (-s)
<i>FCERIA</i> -95 T ^a allele was associated with higher proximal promoter activity in mast cell lines. Presence of T allele in -95 locus was suggested to create additional binding site for GATA-1 transcriptional factor.	Hasegawa et al. (2003) [11]
<i>FCERIA</i> -344 T allele was related to higher proximal promoter activity in mast cell line. Presence of C allele in -344 locus was suggested to create binding motif for MAZ transcriptional factor. Higher histamine release from peripheral basophils obtained from AICU patients with -344 CT genotype (T allele carriers) when compared to -344 CC homozygotes.	Kim et al. (2006) [14], Bae et al. (2007) [15]
<i>FCERIA</i> -95 T>C ^a and -344 C>T ^a polymorphisms was shown to affect proximal promoter activity in additive manner in mastocyte and basophil cell lines; the highest activity was attributed to -95 TT -344 T haplotype, whereas the lowest to -95 CC -344 C one. Preferential binding of Sp1 transcription factor was observed when C allele was present in -344 locus. Presence of the T allele in -344 locus resulted in specific HMG family (HMG-1 and/or -2) binding.	Kanada et al. [22]

FCERIA, the gene encoding for the α -chain of the high-affinity immunoglobulin E receptor (Fc ϵ RI α); GATA-1, GATA binding protein 1; MAZ, Myc-associated zinc finger protein; Sp1, stimulating protein 1; HMG, high-mobility group

^a In papers by Hasegawa et al. [11] and Kanada et al. [22], -95 T>C and -344 C>T polymorphisms were numbered according to transcription start site as -66 T>C and -315 C>T, respectively

presenting cells, a source for cytokines required for the isotype switch during antigen sensitization. Another possibility could be related to basophil-mediated amplification of humoral memory response, a very recently described mechanism, in which basophils activated by antigen binding to Fc ϵ RI-specific IgE complexes on their surface (rechallenge with antigen) can subsequently activate B cells through IL-4, IL-6 and CD40L-CD40 interactions [38]. In this mechanism, SNP-dependent variability of basophil Fc ϵ RI expression might be possibly suggested to affect stimulating effects of basophils on B cells and IgE synthesis.

Nevertheless, it would be interesting to check for a potential pharmacogenetic association between *FCERIA/FCERIB* genetic variants and effects of treatment with anti-IgE therapy, of which omalizumab is a drug more and more commonly used to control persistent refractory moderate-to-severe allergic asthma [39–41]. This treatment modality indirectly affects Fc ϵ RI expression, which downregulates due to binding of circulating IgE by a specific recombinant antibodies [1, 2].

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