Abstract  Fc receptors play a central role in maintaining the homeostatic balance in the immune system. Our knowledge of the structure and function of these receptors and their naturally occurring polymorphisms, including single nucleotide polymorphisms and/or copy number variations, continues to expand. Through studies of their impact on human biology and clinical phenotype, the contributions of these variants to the pathogenesis, progression, and/or treatment outcome of many diseases that involve immunoglobulin have become evident. They affect susceptibility to bacterial and viral pathogens, constitute as risk factors for IgG or IgE mediated inflammatory diseases, and impact the development of many autoimmune conditions. In this chapter, we will provide an overview of these genetic variations in classical FcγRs, FcRLs, and other Fc receptors, as well as challenges in achieving an accurate and comprehensive understanding of the FcR polymorphisms and genomic architecture.

Contents

1 Introduction.................................................................................................................. 275
2 Human FcR Polymorphisms: Location and Functional Implications ....................... 276
   2.1 Single Nucleotide Polymorphisms........................................................................ 276
   2.2 Copy Number Variations (CNVs)....................................................................... 284
3 Human FcR Polymorphisms: Association with diseases........................................... 285
   3.1 Infectious Diseases.............................................................................................. 285
   3.2 Inflammatory and Autoimmune Diseases........................................................... 287
   3.3 Allergic Diseases................................................................................................ 291
4 Association with Response to Antibody Therapy......................................................... 292
5 Conclusions.................................................................................................................. 293
References.................................................................................................................... 293

X. Li · A. W. Gibson · R. P. Kimberly
Department of Medicine, University of Alabama at Birmingham,
Birmingham, AL 35294, USA
e-mail: rpk@uab.edu

M. Daëron and F. Nimmerjahn (eds.), *Fc Receptors*, Current Topics in Microbiology and Immunology 382, DOI: 10.1007/978-3-319-07911-0_13,
© Springer International Publishing Switzerland 2014
1 Introduction

Highly homologous in their extracellular sequences, members of the Fc receptor family have both structural differences as well as allelic variations which impact biological properties and their respective roles in pathophysiology. Investigation over the last two decades has demonstrated regulatory and/or coding single nucleotide polymorphisms (SNP) that change receptor biology through one of three mechanisms: quantitative receptor expression, ligand affinity, or signaling capacity. Emerging data have also demonstrated copy number variation (CNV) in the classical low affinity Fc receptors for IgG. Many of the SNPs and CNVs are associated with pathogenesis, severity, and/or treatment outcome in a range of immune-mediated diseases. Signaling and biology of Fc receptors are discussed in Chapter X and Y. In this chapter, we discuss the germ line variations in the genes encoding Fc receptors and how these variations impact receptor function and association with disease.

2 Human FcR Polymorphisms: Location and Functional Implications

2.1 Single Nucleotide Polymorphisms

Numerous single-nucleotide polymorphisms have been identified through Fc receptor sequence analysis, particularly within the classical low-affinity FcγR cluster located on the long arm of chromosome 1. The allele frequencies of these genetic variants, many of which have not been characterized for function, may differ across different ancestry groups. The more thoroughly studied SNPs with known functional relevance and disease association are presented in Tables 1 and 2.

2.1.1 FcγRIIa (FCGR2A)

A nonsynonymous polymorphism (519G > A, rs1801274) in exon 4 encoding the membrane proximal Ig-like domain of FCGR2A leads to an arginine (R) to histidine (H) change at position 131 and alters receptor affinity for ligand. The R131 and H131 alleles are co-dominantly expressed. The FcγRIIa-H131 allele readily binds human IgG2 while the R131 allele does not effectively bind IgG2 (Salmon et al. 1992; Parren et al. 1992). Studies with IgG3 suggest that the H131 allele may bind IgG3 with moderately greater affinity than the R131 allele (Parren et al. 1992; Bredius et al. 1994). Crystallographic analysis and molecular modeling studies suggest that the H131R position is on the contact interface between receptor-IgG (Maxwell et al. 1999). As the most broadly expressed FcγR across a range of cell types in humans, the variation in ligand affinity has functional relevance in
| Receptor | Genetic variation | Functional property | Disease/trait                                                                 |
|----------|------------------|---------------------|-------------------------------------------------------------------------------|
| FcγRIIa  | R131H (rs1801274)| H131: higher affinity, can bind IgG2 | Infections (Bredius et al. 1993; Endeman et al. 2009; Platonov et al. 1998; Jansen et al. 1999; Yee et al. 2000; Sanders et al. 1994; Bredius et al. 1994; Yuan et al. 2005; Loke et al. 2002; Garcia et al. 2010; Diamantopoulos et al. 2013; Forthal et al. 2007), Autoimmune inflammation (International Consortium for Systemic Lupus Erythematosus et al. 2008; Shrestha et al. 2012; Onouchi et al. 2012; Karassa et al. 2002; Magnusson et al. 2004; Kyogoku et al. 2004; Weersma et al. 2010; Dijstelbloem et al. 1999; Norsworthy et al. 1999; Song et al. 1998; Dijstelbloem et al. 2000; Morgan et al. 2006; van der Pol et al. 2000, 2003; Khor et al. 2011), atopy (Wu et al. 2014) |
|          |                  |                     | **rs10919543** increasing mRNA expression TA (Saruhan-Direskeneli et al. 2013) |
|          |                  |                     | **27Q > W (rs9427397)** unknown KD (Breunis et al. 2013) |
|          |                  |                     | **rs58055840** unknown |
|          |                  |                     | **rs10800309** unknown UC (McGovern et al. 2010; Asano et al. 2009), SS (Lessard et al. 2013) |
|          |                  |                     | **rs12746613** unknown RA (Raychaudhuri et al. 2009) |
|          |                  |                     | **rs6658353** unknown SS (Lessard et al. 2013) |
| FcγRIIb  | I232T (rs1050501)| T232: altered partition to lipid rafts; altered signaling capability | SLE (Kono et al. 2005; Chu et al. 2004; Chen et al. 2006), atopy (Wu et al. 2014) |
|          | 2B.1/2B.4* (rs3219018) | 2B.4: higher promoter activity/ expression | SLE (Su et al. 2004; Blank et al. 2005; Olferiev et al. 2007), KD (Breunis et al. 2013) |
|          | rs2125685 | unknown | Periodontitis (Sugita et al. 2012) |
| FcγRIIC | STP/Q13 (rs10917661) | STP: pseudogene; Q13: expression | ITP (Breunis et al. 2008), SLE (Li et al. 2013), KD (Breunis et al. 2013) |
|          | CNV | altered protein expression level | ITP (Breunis et al. 2008), SLE (Li et al. 2013) |
| Receptor | Genetic variation | Functional property | Disease/trait |
|----------|-------------------|---------------------|--------------|
| FcγRIIIa | V158F rs396991    | V158: higher affinity for IgG1, IgG3 | SLE (Wu et al. 1997; Edberg et al. 2002; Koene et al. 1998), RA (Morgan et al. 2006), GPA (Dijstelbloem et al. 1999), Lupus nephritis (Jonsen et al. 2007) |
|          | CNV rs445509      | Altered protein expression level | anti-GBM disease (Zhou et al. 2010) |
| FcγRIIIb | NA1/NA2<sup>b</sup> | NA1: higher affinity | SLE (Hatta et al. 1999), ITP (Foster et al. 2001) |
|          | SH                | unknown              | unknown |
|          | CNV               | Altered protein expression level | SLE (Willcocks et al. 2008), ANCA vasculitis (Tse et al. 2000; Niederer et al. 2010), SS (Nossent et al. 2012) |

<sup>a</sup> Promoter haplotype. 2B.1: -120G-386T; 2B.4: -120C-386A
<sup>b</sup> Coding haplotype. NA1: 141G 147C 227A 349G; NA2: 141C 147T 227G 349A

TA: Takayasu’s arteritis; KD: Kawasaki disease; UC: ulcerative colitis; SS: Sjögren’s Syndrome; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ITP: idiopathic thrombocytopenia purpura; GPA: Granulomatosis with polyangitis (Wegener’s granulomatosis); anti-GBM disease: Anti-glo-merular basement membrane (anti-GBM) antibody disease; ANCA: anti neutrophil cytoplasmic antibodies
| Receptor | Genetic variation | Functional property | Disease/trait |
|----------|------------------|---------------------|---------------|
| FcεRI-α  | −66T/C (rs2251746) | −66T: higher promoter activity/expression | AD (Hasegawa et al. 2003), asthma (Zhou et al. 2012), high IgE (Weidinger et al. 2008; Granada et al. 2012) |
|          | −315C/T (rs2427827) | −315T: higher promoter activity/expression | Chronic urticarial (Kim et al. 2006; Bae et al. 2007), asthma (Shikanai et al. 1985; Potaczek et al. 2006; Zhou et al. 2012) |
| FcεRI-β  | E237G            | unknown             | Atopy, asthma (Zhang et al. 2004; Yang et al. 2014), nasal allergy (Kim et al. 2007; Laprise et al. 2000; Nagata et al. 2001) |
|          | I181L            | unknown             | Atopy (Li and Hopkin 1997) |
|          | −109C/T          | unknown             | High IgE (Hizawa et al. 2000), asthma (Kim et al. 2006; Yang et al. 2014) |
| FcεRII   | R62 W (rs2228137) | W62: resistance to proteolytic cleavage | Asthma (Laitinen et al. 2000) |
|          | rs3760687        | unknown             | High IgE (Sharma et al. 2014) |
| FcαRI    | S248G            | G248: higher IgA-mediated activation | SLE (Wu et al. 2007) |
| FCRL1    | rs4971154        | unknown             | T1D (Pagnol et al. 2011) |
| FCRL3    | rs7528684        | Altered gene expression | SLE, RA, AITD (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013); (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013); T1D (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013); MS (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013); Endometriosis (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013) |
|          | rs7522061        | unknown             | MS (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013) |
|          | rs2282288        | unknown             | GD (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013) |
|          | rs11264798       | unknown             | T1D (Osuga et al. 2011; Teles et al. 2011; Szczepanska et al. 2013) |
| FCRL4    | rs2777963        | unknown             | AS (Zeng et al. 2012) |

(continued)
| Receptor | Genetic variation | Functional property | Disease/trait |
|----------|------------------|---------------------|---------------|
|          | rs14335          | unknown             | AS (Zeng et al. 2012) |
|          | rs10489674       | unknown             | AS (Zeng et al. 2012) |
| FCRL5    | rs12036228       | unknown             | AS (Tang et al. 2009) |
|          | rs6427384        | unknown             | AS (Tang et al. 2009) |
| FcRn     | VNTR\(^a\)       | altered promoter activity/expression | unknown |

\(^a\) VNTR: variable number of tandem repeats
AD: atopic dermatitis; T1D: type-1 diabetes; AITD: autoimmune thyroid disease; MS: multiple sclerosis; GD: Graves’ disease; AS: ankylosing spondylitis
determining cellular interactions with IgG antibodies, including the clearance of IgG2 immune complexes. For example, neutrophils from FcγRIIa-H131 homozygous donors are much more effective than neutrophils from R131 homozygous donors in phagocytosing IgG2-opsonized particles (Bredius et al. 1993).

Several FCGR2A SNPs, including rs1801274 encoding R131H (International Consortium for Systemic Lupus Erythematosus 2008), as well as several variants in non-coding regions, including rs10919543 (Saruhan-Direskeneli et al. 2013), rs12746613 (Raychaudhuri et al. 2009), rs10800309 (McGovern et al. 2010; Asano et al. 2009), rs6658353 (Lessard et al. 2013), and rs6427609 (Kettunen et al. 2012), have been associated with disease phenotypes in various genome-wide association studies (GWAS). These disease association studies, based on high throughput genotyping technologies, suggest that variation in FcγRIIa biology may contribute to a number of human disease phenotypes. However, not all variants identified through such studies have an obvious function or relationship to biological processes, and direct inference of pathophysiology requires further study. In some cases, SNP-based associations may be tagging linkage disequilibrium (LD) blocks. Given the segmental duplication in the classical low affinity FCGR cluster and the consequent high degree of genomic sequence homology, this region is not technically amenable to efficient genotyping with array-based strategies. Thus, genotyping coverage in genome-wide association studies is not optimal because of difficulty in accurate probe design and position assignment.

2.1.2 FcγRIIb (FCGR2B)

Some nonsynonymous coding SNPs in the FcR cluster affect the signaling capacity of the expressed receptor. In the FCGR2B gene locus, a nonsynonymous T > C SNP (rs1050501) encodes an isoleucine (I) to threonine (T) substitution at position 187 in the transmembrane domain; this variant is also known as I/T232 when the signal peptide is included in the numbering (Kyogoku et al. 2002; Li et al. 2003). The FcγRIIb-187threonine allele, which is less efficient in trans-locating into lipid rafts in the plane of the cell membrane, may result in decreased quantitative participation of FcγRIIb in the assembly of lipid raft-based signaling complexes with a resultant decreased inhibitory potential (Kono et al. 2005; Floto et al. 2005).

Su et al. identified a promoter haplotype (rs3219018) in FcγRIIb that alters receptor expression (Su et al. 2004). The less common promoter haplotype (−386C-120A) showed increased binding of transcription factors GATA4 and Yin-Yang 1, leading to higher receptor expression than found with the more frequent haplotype (−386G-120T) (Su et al. 2004a, b; Blank et al. 2005). Of note, sequence analysis of these promoter variants has revealed nearly identical sequence in the proximal promoter region of FCGR2C, thus underscoring the important consideration of the potential for expression of both receptors.
2.1.3 FcγRIIc (FCGR2C)

FCGR2C, often considered a pseudogene, has received less attention than other Fc receptors. The nonsynonymous SNP (202T>C, rs10917661) in its first extracellular domain changes the common allele (202T), which encodes a translation termination codon at residue position 13, to 202C, which encodes an open reading frame (ORF) for glutamine. The FcγRIIc-ORF allele produces an ITAM-containing activating receptor that has been detected on NK cells (Metes et al. 1998, 1999; Stewart-Akers et al. 2004) and B cells (Li et al. 2013). Functionally, NK cells bearing the ORF allele are capable of clearing anti-FcγRII coated particles through reverse antibody-mediated cellular cytotoxicity (ADCC) (Ernst et al. 2002; Breunis et al. 2008). On B cells, the FcγRIIc-ORF allele counterbalances the negative feedback of FcγRIIb on BCR signaling, resulting in enhanced B cell responsiveness including upstream signaling events such as tyrosine kinase phosphorylation and calcium transients, and integrated cell programs such as antibody production (Li et al. 2013).

2.1.4 FcγRIIIa (FCGR3A)

Similar to FcγRIIa, FcγRIIIa also has co-dominantly expressed alleles that affect receptor affinity for ligand. In the second extracellular domain of FCGR3A, a point substitution of T to G at nucleotide 559 (rs396991) changes the phenylalanine (F) at amino acid position 158 to valine (V). The FcγRIIIa-158V allele (also known as 176 V when the leader sequence is included) displays higher affinity for IgG1 and IgG3 relative to the 158F (176F) allele. The 158V form is also capable of binding IgG4, while the 158F allele is not (Wu et al.1997; Koene et al. 1997). NK cells from FcγRIIIa-158V (high binder) homozygous donors exhibit increased calcium influx, greater CD25 expression, and faster apoptosis than those cells from FcγRIIIa-158F (low binder) homozygous donors (Wu et al. 1997).

2.1.5 FcγRIIIb (FCGR3B)

The GPI-anchored FcγRIIIb, mainly expressed on neutrophils, has three different allotypic variants, known as NA1, NA2, and SH. The neutrophil antigen (NA) variants NA1 and NA2 are a product of five nonsynonymous SNPs in the first Ig-like domain, with an asparagine to serine switch at amino acid position 65 resulting in altered glycosylation and reduced affinity in the NA2 allele (Ravetch and Perussia 1989; Salmon et al. 1990). FcγRIIIb-NA1 exhibits higher affinity and more efficient phagocytosis of IgG1 and IgG3 opsonized particles compared to the NA2 allele (Salmon et al. 1990). The SH allele results from an alanine to aspartic acid substitution at position 78 and is observed in the context of the NA2 allele (Bux et al. 1997). The exact function of the SH allele is not yet known.
2.1.6 FcαRI (FCAR)

FCAR (CD89) encodes the human IgA receptor FcαRI. A common SNP (844A > G) was identified through direct sequencing of the coding region of FCAR (CD89) (Jasek et al. 2004; Wu et al. 2007). This transition changes amino acid codon 248 in the cytoplasmic domain from serine to glycine, resulting in enhanced cellular functions. For example, when equivalently stimulated with human IgA, neutrophils homozygous for the FcαR-G248 allele produce significantly higher levels of IL-6 compared to neutrophils from homozygous FcαR-S248 individuals. In the absence of FcR γ-chain pairing, FcαR-S248 allele fails to induce pro-inflammatory cytokines. In contrast, FcαR-G248 maintains signaling capacity even without the FcRγ, producing both IL-6 and TNFα. The increased activity of the G248 form may reflect, at least in part, its enhanced association with the Src family kinase, Lyn (Wu et al. 2007).

2.1.7 FcεRI (FCER1A/B/G)

The high affinity Fc receptor for IgE, FcεRI, has SNPs in the promoter region of the receptor α-chain (FCER1A). Through mutational screening of the proximal promoter, −95T > C (also referred to as −66) and −344C > T (also referred as −335) SNPs have been identified in several ethnicities (Shikanai et al. 1985; Hasegawa et al. 2003; Potaczek et al. 2006). Functionally, the −95T allele has greater GATA-1 binding, increased transcription of FCER1A message, and enhanced FcεRI protein expression on mast cells compared to the −95C allele (Hasegawa et al. 2003; Nishiyama 2006). Similarly, the −344C to T transition increases the binding of Myc-associated zinc finger (MAZ) transcription factors, resulting in increased protein expression (Kim et al. 2006; Bae et al. 2007). Furthermore, these two SNPs affect proximal promoter activity in an additive manner, with the highest activity attributed to the −95T-344T haplotype (Kanada et al. 2008).

The other two subunits of the IgE receptor, the FcεRIγ and FcεRIβ, have also been screened for genetic variations. Although the FCER1G gene is highly conserved (Wu et al. 2002), the FCER1B gene (also named MS4A2) contains several SNPs in the promoter region. The −426C-654T haplotype has higher binding of Yin-Yang 1 and higher transcription activity relative to the −426T-654C haplotype (Nishiyama et al. 2004).

The low affinity receptor for IgE, FcεRII (CD23), carries a functional SNP at position 62 in exon 4, resulting in an arginine (R) to tryptophan (W) substitution. The less common W62 allele is resistant to proteolytic shedding while the common R62 allele is known to be cleaved by a wide range of proteases and shed from cell surface (Meng et al. 2007). Soluble FcεRII has mitogenic properties, promoting the survival and differentiation of germinal center B cells (Liu et al. 1991). In vitro experiments have also suggested that the R62 W SNP affects IgE production through affecting Erk phosphorylation, which results in altered B cell responsiveness to IL-4 (Chan et al. 2014).
2.1.8 FcRLs

The FCRL genes encoded at the autoimmunity-linked 1q23 locus are highly polymorphic with SNPs and many mRNA splice isoforms identified for each gene locus. However, proteins corresponding to most of the splice isoforms have not been identified (Davis et al. 2002). Numerous SNPs have been identified within the FCRL coding regions, introns, the upstream promoter and the downstream non-coding regions. With the exception of the FCRL3 -T169C promoter SNP (rs7528684), which alters an NF-kB binding site and results in increased expression of the FCRL3 mRNA and protein in PBMC, CD19 + B cells and CD8 + T cells subsets (Kochi et al. 2005; Gibson et al. 2009; Chu et al. 2011), little is known about functional correlates in FCRL family SNPs. Nevertheless, many studies have identified association between autoimmune disease and genetic variation in FCRL genes suggesting an important role in disease. Several case-control studies of FCRL3 polymorphisms in autoimmunity are summarized in a recent review (Chistiakov and Chistiakov 2007).

2.1.9 FcRn (FCGRT)

Although no common functional SNPs have been identified to date in FCGRT, the gene that encodes the neonatal Fc receptor, FcRn, a variable number of tandem repeats (VNTR) region in the promoter region consists of one to five repeats of a 37-bp motif (VNTR1-VNTR5) (Sachs et al. 2006). VNTR3 is the most common allele in Caucasian and Asian populations, followed by VNTR2. In vitro experiments have shown that VNTR3 has stronger transcriptional activity compared to VNTR2, resulting in more FcRn expression. Under acidic conditions, monocytes homozygous for VNTR3 showed increased IgG binding capacity compared to monocytes derived from VNTR2/VNTR3 heterozygous individuals (Sachs et al. 2006).

2.2 Copy Number Variations (CNVs)

Allotyping individual for the NA1 and NA2 alleles of FCGR3B led to the earliest observed copy number variation (CNV) in the classical low affinity FCGR cluster. Lack of both alleles identified FCGR3B deficiency (Clark et al. 1990; Huizinga et al. 1990), and duplication of the gene was inferred when all three alleles of FCGR3B (NA1, NA2 and SH) were simultaneously detected in the same individual (Koene et al. 1998). Copy number variation of FCGR3B correlates with the expression level of FcyRIIIb and with the capacity of neutrophils to phagocytose immune complexes (Willcocks et al. 2008).
CNV has also been reported for *FCGR2C* and *FCGR3A*. Because *FCGR2C* and *FCGR3B* are adjacent in the genome (Fig. 1), CNV of both genes is highly correlated (de Haas et al. 1995; Reilly et al. 1994). Copy number of the *FCGR2C*-ORF allele correlates with FcγRIIc expression levels and consequently, activation status of NK cells (Breunis et al. 2008) and B cells (Li et al. 2013). Similarly, CNV of *FCGR3A* correlates with FcγRIIIa expression on NK cells (Breunis et al. 2009).

3 Human FcR Polymorphisms: Association with diseases

The central role of Fc receptors in supporting an appropriate humoral immune system has been demonstrated by numerous ex vivo and in vivo studies, in both human and model animals. Often one allele enhances activation and/or net immune system activity while the second allele tends to be less effective in eliciting responses, such as clearance and processing of immune complexes or antibody opsonized particles. Thus, functional FcR polymorphisms may significantly influence effector cell functions, thus providing diversity in host responses pertinent to many infectious, inflammatory and autoimmune diseases. For many SNPs, however, especially when they are in noncoding regions, the direct impact on biological function is not known and the potential influence on pathophysiology is ambiguous. An understanding of these associations and their implications for disease processes awaits further insight into the pertinent genomic architecture of the overall immune response.

3.1 Infectious Diseases

3.1.1 Infection with Encapsulated Bacteria

Often working in synergy with the complement system, FcγR-mediated clearance of antibody-coated microbes and FcγR-triggered inflammatory cytokine release are important mechanisms in eliminating infectious agents. Since human IgG2 is
relatively inefficient in initiating the complement cascade, the FcγRIIa-131H allele is the primary leukocyte receptor capable of effectively clearing IgG2-coated microbes, which is important in host defense against encapsulated bacteria such as *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitidis* (Bredius et al. 1993; Jefferis and Kumararatne 1990; Endeman et al. 2009; Platonov et al. 1998; Jansen et al. 1999). In the context of *Strep pneumonia* pneumonia, the FcγRIIa-131R allele, which fails to bind IgG2, may be over-represented in bacteremic patients, and in one study, the most severely infected bacteremic patients, who died within 1 week of hospitalization, were all homozygous for the R131 allele (Yee et al. 2000). Similarly, the FcγRIIa-131R allele is associated with increased infection by *Hemophilus influenzae* and *Neisseria meningitidis* in multiple bacterial respiratory diseases and sepsis (Endeman et al. 2009; Platonov et al. 1998; Sanders et al. 1994; Bredius et al. 1994; Yuan et al. 2005). Of note, FcγRIIa also binds C-reactive protein with allele sensitivity reciprocal to IgG2 (Stein et al. 2000). High levels of CRP during infection may contribute to the clearance of IgG2-coated microbes by the R131 allele by opsonizing encapsulated bacteria and subsequently activating the complement mediated clearance (Weiser et al. 1998), which may compensate, at least in part, for the lack of FcγR-IgG2 mediated clearance in patients with the R131 allele.

### 3.1.2 Periodontitis

Periodontitis, an infectious disease caused by pathogenic anaerobic bacteria in the periodontium and the corresponding host response, is influenced by a combination of behavioral, environmental and genetic factors. Several types of FcγR-bearing cells are found in periodontal tissues, including neutrophils, lymphocytes and dendritic cells (Yuan et al. 1999). Functional studies largely focused on neutrophils have demonstrated that neutrophils homozygous for the FcγRIIa-131H allele were more efficient in bacterial phagocytosis, degranulation and elastase release (Nicu et al. 2007). In the same study the homozygous FcγRIIa-H131 patients also showed more bone loss than those with the H/R or R/R allotypes. Kobayashi et al. has also reported that neutrophils carrying the FcγRIIib-NA2 allele showed lower reactivity to IgG1/IgG3 coated periodontopathic bacteria and induced weaker oxidative burst (Kobayashi et al. 2000).

Association studies calculating the clinical relevance of FcγR polymorphisms in periodontitis have reported mixed results, complicated by the difference in size and ethnicity of the population studied and the inconsistent definitions of disease stage and progression. A recent meta-analysis aggregating 17 studies reported modest association of FcγRIIa-131R with aggressive periodontitis in Asians, relatively strong association of the FcγRIIib-NA1/NA2 polymorphism with both aggressive and chronic periodontitis, and a statistically insignificant relationship between the FcγRIIIa-F158 V and periodontitis (Song and Lee 2013). In studies of the distribution of the inhibitory FcγRIIb variants, significant enrichment of the FcγRIIb-232T allele in patients with aggressive periodontitis compared to both
chronic periodontitis patient and healthy control groups occurs in Japanese periodontitis patients (Yasuda et al. 2003). Furthermore, the composite genotype of FcγRIIb-232T plus FcγRIIIb-NA2 was strongly associated with aggressive periodontitis. The large number of B cells (Yuan et al. 1999) and the elevated antibody level (Horino et al. 1989) in periodontal lesions, as well as our understanding of the biology of the FcγRIIb-232T allele make the link between FcγRIIb-232T and periodontitis biologically plausible.

Besides the well-known polymorphisms, several other SNPs in the FcγR cluster have been identified in association with periodontitis. For example, the FCGR2B-nt645 + 25A/G (rs2125685) SNP in intron 4 was reported in Japanese patients and was related to changes in receptor expression level and severity of periodontitis (Sugita et al. 2012). A little studied SNP in FCGR3A (rs445509) was associated with chronic periodontitis in a Chinese population (Chai et al. 2010). Further study of these variants may elucidate their function and contribution to disease.

3.1.3 Virus Infection

Variants influencing Fc receptor function are also relevant in host defense mechanisms for virus infections. Dengue virus may co-opt Fcγ receptors for cell entry when the antibody-opsonized virus particles are phagocytized by FcγR-bearing myeloid cells, establishing infection in the phagocytes (Moi et al. 2010; Littaua et al. 1990; Garcia et al. 2011). Several studies have suggested the FcγRIIa-R131 allele may have a protective effect in Dengue virus infection (Loke et al. 2002; Garcia et al. 2010). The FcγRIIa-R131H SNP is one important factor in host defense, as it is also reported to be relevant in infections with A/H1N1 influenza (Zuniga et al. 2012), severe acute respiratory syndrome (SARS)-coronavirus (Yuan et al. 2005), and Epstein–Barr virus (Diamantopoulos et al. 2013). In human immunodeficiency virus (HIV) infection, patients with homozygous low affinity R131 allele showed the highest rate of disease progress (Forthal et al. 2007). The FcγRIIIa-V158F genotype also correlates with the development of Kaposi’s sarcoma in HIV-infected patients (Forthal et al. 2007; Lehrnbecher et al. 2000).

3.2 Inflammatory and Autoimmune Diseases

3.2.1 Vasculitides

The vasculitides are a group of disorders that involve inflammation of the blood vessels. Although the etiology of vasculitis is often not clear, vascular inflammation can be immunologically mediated, triggered by immune complexes, anti-neutrophil cytoplasmic antibodies, anti-endothelial cell autoantibodies as well as by cell-mediated processes. The classification of the vasculitides is typically based
on the size of the affected vessel. Granulomatosis with polyangiitis (GPA), formerly known as Wegener’s granulomatosis, is a type of neutrophil mediated vasculitis affecting small and medium sized vessels. GPA is often characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) (Nolle et al. 1989). Engagement of both ANCA target and Fc receptors on myeloid cells by ANCA elicits production of interleukin-8, a neutrophil chemotactic factor, and a series of effector programs such as oxidative burst, degranulation and release of neutrophil extracellular traps (NETs) (Ralston et al. 1997; Porges et al. 1994; Kessenbrock et al. 2009; Sangaletti et al. 2012). No clear association between GPA susceptibility and the FcγRIIIa allotype has been demonstrated although some evidence suggests a relationship to the likelihood of relapsing disease (Edberg et al. 1997; Tse et al. 1999, 2000). FcγRIIIb, the numerically predominant FcγR on neutrophils, is the major receptor interacting with anti-PR3 IgG ANCA (Kocher et al. 1998), and FCGR3B CNV has been associated with GPA (Fanciulli et al. 2007). The FcγRIIIb-NA1 allele, known to induce stronger neutrophil activation than the NA2 allele (Salmon et al. 1990), has similar allele frequencies in GPA and healthy populations, suggesting no role in overall disease risk. However, the presence of the NA1 allele is associated with the development of severe renal damage in GPA patients (Neira et al. 1996; Kelley et al. 2011).

The recent identification of IgA ANCA in GPA, in addition to IgG ANCA, led to the investigation of the involvement of FcαRI in GPA pathogenesis. Indeed, the FcαRI-248G variant, which induces an augmented inflammatory response to IgA, was associated with overall susceptibility to GPA, as well as predisposition to severe renal disease (Kelley et al. 2011).

Kawasaki disease affects medium-sized blood vessels most commonly in children under 5 years of age. Genome wide association studies have identified an association between Kawasaki disease and the FCGR2A locus with the 131H variant conferring elevated disease risk (Shrestha et al. 2012; Onouchi et al. 2012). It is reasonable to speculate the FcγRIIa-131H bearing leukocytes are more pro-inflammatory in the setting of Kawasaki disease, although direct experimental evidence waits to be established. One might also anticipate an association between IgG receptor variants and intravenous immunoglobulin (IVIG), the only proven therapy for Kawasaki disease. Indeed, in Japanese patients, those with the FcγRIIa-131H allele responded more efficiently to IVIG administration. Patients with the 131R allele were more likely to develop coronary lesions even after treatment (Taniuchi et al. 2005). Consistent with the notion that tilting the immune system towards inflammation might be associated with disease expression, the FCGR2C-ORF SNP was recently reported to be enriched in Kawasaki disease patients (Breunis et al. 2013).

Takayasu’s arteritis is a rare form of large vessel vasculitis. A recent GWAS in Turkish and North American Takayasu’s arteritis patients identified a noncoding SNP in the FCGR2A/FCGR3A locus (rs10919543) as a susceptibility marker, which appeared to have a regulatory effect on FCGR2A transcript expression (Saruhan-Direskeneli et al. 2013).
Several other forms of chronic inflammatory diseases have been reported to have associations with the FCGR cluster. The FCGR2A/2C region has been related to susceptibility to ulcerative colitis, one sub-phenotype of inflammatory bowel disease, in two GWA studies (McGovern et al. 2010; Asano et al. 2013). In addition to the well-known FcγR-R131H variant, the rs10800309 variant in this locus awaits further work to determine potential functional relevance.

### 3.2.2 Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by autoantibodies and immune complexes. Although the etiology of SLE is unknown, many genes play a role in the susceptibility to and severity of the disease, and GWAS and candidate genes studies have identified the FCGRs as important contributors to the SLE diathesis (Harley et al. 2009).

A GWAS study of Europeans confirmed the association of FCGR2A (rs1801274; 519G > A encoding R131H) with SLE (International Consortium for Systemic Lupus Erythematosus 2008). This nonsynonymous SNP is a risk factor for lupus nephritis and systemic lupus erythematosus in African Americans (Salmon et al. 1996; Edberg et al. 2002), Caucasians (Manger et al. 2002; Karassa et al. 2002; Magnusson et al. 2004; Kyogoku et al. 2004) and Asians (Siriiboonrit et al. 2003; Lee et al. 2002; Chu et al. 2004), as well as for myasthenia gravis in Caucasians (Weersma et al. 2010; van der Pol et al. 2003). Homozygosity for the transmembrane 187T variant of FcγRIIb is also associated with SLE susceptibility in Japanese (Kyogoku et al. 2002), Chinese (Chu et al. 2004) and Thais (Siriiboonrit et al. 2003). Interestingly, the 187T allele has a lower frequency in European Americans and is not associated with SLE in either this ancestry group or in African Americans where the frequency of 187T is similar to that of Asians (Li et al. 2003; Magnusson et al. 2004). Whether this difference represents, less statistical power for detection of association in these groups or an epistatic effect is not certain. The FcγRIIb-187T allele may be a risk factor for anti-GBM disease in Chinese (Zhou et al. 2010) while a promoter haplotype, 2B.4 (−386C −120A), which alters FCGR2B gene expression is associated with SLE (Su et al. 2004). In a second patient population, homozygosity of the −386C allele alone (also referred to as −343C) affirmed an association of promoter variants with SLE (Blank et al. 2005). CNV in this receptor cluster, including the FCGR2C-ORF allele, may be associated with SLE in patients of European and African ancestry (Li et al. 2013).

The low IgG binding FcγRIIIa-158F is associated with SLE and with lupus nephritis (Wu et al. 1997; Karassa et al. 2002; Jonsen et al. 2007; Dong et al. 2013) in multiple ancestry groups including Europeans, African Americans (Edberg et al. 2002; Koene et al. 1998), Chinese (Chu et al. 2004), and Japanese (Kyogoku et al. 2002). Interestingly, homozygosity for the high IgG binding −158 V allele is a significant predictor of end-stage renal disease in a multiethnic group of SLE patients (Alarcon et al. 2006). Both FcγRIIIb CNV and NA1/NA2 alleles may be associated
with SLE in UK Caucasians (Willcocks et al. 2008), Thais (Siriboonrit et al. 2003), Japanese (Hatta et al. 1999), and Spanish (Gonzalez-Escribano et al. 2002).

The $-169C > T$ SNP (rs7528684) in FCRL3, which alters an NFκB binding site and is associated with FCRL3 mRNA and surface protein expression, is associated with autoimmunity in some ethnic groups. Associated with SLE, RA, and AITD in Japanese (Kochi et al. 2005; Gibson et al. 2009), this variant is not associated with these conditions in other ethnicities suggesting that it is not a general autoimmunity risk factor (Christakov and Christakov 2007). The $-169C > T$ SNP is not associated with SLE in Chinese (You et al. 2008), Koreans (Choi et al. 2006), or Mexican patients with childhood-onset SLE (Ramirez-Bello et al. 2013), but the association with the presence of autoantibodies in Polish SLE patients suggests a possible role in production of autoantibodies (Piotrowski et al. 2013). Results of meta-analyses differ on whether the $-169C > T$ is associated with SLE in different ethnicities (Breunis et al. 2013; Mao et al. 2010; Song et al. 2013), and the mechanism(s) through which this variant may contribute to SLE remains unclear.

3.2.3 Rheumatoid Arthritis and Juvenile Idiopathic Arthritis

Evidence for the contributions of the classical low-affinity Fcγ receptors to Rheumatoid Arthritis suggests that several polymorphisms may be associated with RA manifestations in different ethnic groups, although associations are not always consistent. While GWAS indicated that FCGR2A is associated with RA (Raychaudhuri et al. 2009), candidate gene studies suggest the FCGR3A is associated with RA (Morgan et al. 2000; Morgan et al. 2003) and a role for FCGR2C is unclear.

The $-169C > T$ promoter SNP in FCRL3 is associated with RA in Caucasians and Chinese (Thabet et al. 2007; Eike et al. 2008; Maehlen et al. 2011; Wu et al. 2010), with JIA in Mexicans (Ramirez-Bello et al. 2013), and with JIA in Norwegian patients (Eike et al. 2008). This SNP has been correlated with increased FCRL3 surface expression on Tregs of patients with erosive RA (Bajpai et al. 2012), and the $-169CC$ genotype may be correlated with radiographic severity in Korean RA patients (Han et al. 2012). A more detailed review of Fc receptor associations and rheumatoid arthritis is discussed in Chapter XX.

3.2.4 Spondyloarthropathies

The rs2777963T > C, rs14335A > G and rs10489674C > T polymorphisms in FCRL4 have been associated with susceptibility and severity of ankylosing spondylitis (AS) in Han Chinese (Zeng et al. 2012). Similarly, in FCRL5 two nonsynonymous SNPs, rs12036228C > T and rs6427384T > C in exon 5 and exon 7, respectively, and their C-T haplotype were found to be associated with
ankylosing spondylitis in HLA-B27 positive Han Chinese, suggesting a role in AS (Tang et al. 2009). However, the role, if any, of these SNPs in FCRL4 and 5 expression or function is unclear.

### 3.2.5 Diabetes Mellitus and Autoimmune Endocrinopathies

Several studies have found association between autoimmune endocrinopathies and SNPs in FCRL family members, although potential underlying mechanisms remain elusive. In a recent study of Type 1 Diabetes (T1D) the C-allele of FCRL1 rs4971154 was strongly associated with the presence of the IA-2A autoantibody in serum suggesting a role in production of autoantibodies (Mao et al. 2010). Although the FCRL3 -169C > T SNP was not associated with T1D in several studies of Caucasians (Eike et al. 2008; Owen et al. 2007; Duchatelet et al. 2008), a recent study of 8,506 T1D patients in the United Kingdom found a strong negative association between the C allele and anti-IA-2A autoantibody- positive T1D (Mao et al. 2010). The mechanism of association remains unclear.

In autoimmune thyroid disease, Owen et al. found modest association of the 3’UTR C > A SNP rs2282288 with Grave’s Disease in Europeans (Owen et al. 2007). The -169TT promoter genotype of rs7528684 was associated with remission in Japanese AITD patients (Inoue et al. 2012), and with protection against Grave’s Disease in Chinese (Gu et al. 2010). A potential role for FCRL3 in production of autoantibodies is supported by the observations that the rs11264798C > G and rs7528684C > T SNPs are associated with thyroid peroxidase autoantibody (TPOA) positivity in GD and anti-IA-2A positivity in T1D (Plagnol et al. 2011), while the rs7522061T > C SNP is associated with anti-ZnT8A positivity (autoantibody to the zinc transporter 8 in islet cells) in T1D patients (Howson et al. 2012).

### 3.2.6 Multiple Sclerosis

The FCRL3 -169C > T SNP (rs7528684) has been associated with multiple sclerosis in a Spanish cohort (Martinez et al. 2007; Matesanz et al. 2008). While the T allele of the nonsynonymous coding SNP (rs7522061), which results in the N28D change, was found to be protective in Spanish, the G allele was a risk factor for MS in patients in the United Kingdom (Matesanz et al. 2008).

### 3.2.7 Inflammatory Bowel Disease

Despite its association with many autoimmune disorders in different ethnicities, the -169C > T SNP appears not to be associated with risk for ulcerative colitis, Crohn’s disease or primary sclerosing cholangitis (Eike et al. 2008), or with Inflammatory Bowel Disease (Martinez et al. 2007).
3.3 Allergic Diseases

Allergic diseases are a type of hypersensitivity characterized by mast cell activation and IgE-mediated inflammation. The high-affinity IgE receptor expressed on mast cells, FcεRI, has long been considered a candidate gene in allergic diseases. Multiple studies have established a consistent genetic association between allergies and the promoter variants of FcεRI α-chain. The $-66T > C$ and/or the $-315C > T$ SNPs are associated with atopic dermatitis, chronic urticaria, asthma, and high serum IgE levels (Hasegawa et al. 2003; Potaczek et al. 2006; Kim et al. 2006; Bae et al. 2007; Zhou et al. 2012; Niwa et al. 2010). The $-66T > C$ SNP was highlighted as the strongest hit in two GWA studies with high IgE levels (Weidinger et al. 2008; Granada et al. 2012). These genetic findings may be explained by functional studies that have demonstrated that both SNPs amplify transcription activity, increasing FcεRI expression on mast cells and basophils (Hasegawa et al. 2003; Kanada et al. 2008), and the well-established observation that surface FcεRI expression correlates positively with circulating IgE levels (MacGlashan 2005).

Similarly, several SNPs in the FcεRI β-chain are associated with allergic inflammatory diseases such as atopy, asthma, and nasal allergy (Nishiyama et al. 2004; Zhang et al. 2004; Laprise et al. 2000; Nagata et al. 2001; Li and Hopkin 1997; Hizawa et al. 2000; Kim et al. 2006, 2007; Yang et al. 2014). Functional properties of these SNPs are not known.

The low-affinity IgE receptor on B cells, FcεRII (CD23), is important in regulating IgE production and B cell differentiation. The R62W alteration in the FCER2 gene, that yields increased IgE binding and augmented ERK signaling (Chan et al. 2014), is associated with elevated serum IgE levels and an increased risk of severe asthma exacerbation in children (Laitinen et al. 2000; Koster et al. 2011; Tantisira et al. 2007). A promoter SNP in the FCER2 gene, rs3760687, associated with increased total serum IgE (Sharma et al. 2014), may alter the activity of the transcription factors Sp1 and Sp3, leading to modulation of FcεRII expression (Potaczek et al. 2009).

Even though IgE and IgE receptors have been known to be the major players in allergic inflammation, allergen-specific IgG and FcγRs also play a role (Kaneko et al. 1995; Jonsson et al. 2012; Williams et al. 2012; Lau et al. 2005; Bruhns et al. 2005). In a candidate gene study, both the FcγRIIa-R131H and the FcγRIIb-I187T SNPs have been associated with atopy (Wu et al. 2014). In this context, it is conceivable that FcγRIIa-H131 allele may clear allergen-IgG2 immune complexes more efficiently, preventing inflammation and tissue damage. Whether allergen-specific IgG2 levels vary in accordance with FcγRIIa polymorphisms is unknown. Furthermore, the FcγRIIb-187T allele may not be as effective in negatively regulating BCR function, resulting in increased B cell IgE production. Crosstalk between FcγRIIb and FcεRI on mast cells is also a possibility.
4 Association with Response to Antibody Therapy

The efficacy of therapeutic monoclonal antibodies used in autoimmune diseases to induce ADCC and deplete autoreactive B lymphocytes from circulation depends, at least in part, on the strength of the interaction of activating FcγRs with the therapeutic antibody on the opsonized target cells. The FcγRIIIa -158F/V polymorphism influences the efficacy of rituximab treatment, which targets the CD20 surface protein on B cells, with patients homozygous for the high binding -158 V allele showing the best response (Robledo et al. 2012; Cooper et al. 2012). The precedent that alleles which alter binding and function of FcγRIIa and FcγRIIIa may affect the efficacy of antibody therapy is an important principle in antibody-based therapeutics. A more extensive discussion of the role of Fc receptors in the use of therapeutic antibodies is presented in Chapter XX, “FcR and therapeutic antibodies”.

5 Conclusions

Genetic variations in human Fc receptors, through their impact on antibody-mediated mechanisms, contribute to individual and population-based host defense and susceptibility to a range of human diseases. Fc receptor polymorphisms modulate the effectiveness of immune system in defense against invading pathogens by regulating immune cell activities. They also impact the handling of immune reactants and the threshold of immune tolerance. Complex clinical phenotypes, such as autoimmunity or allergy, involve multiple genetic and environmental factors, and the subtle regulatory effects of various naturally occurring polymorphisms are compounded in their impact over time. Accurate assessment of the contributions of Fc receptor polymorphisms to immune system function and clinical phenotype requires a careful understanding of the genomic structure, sequence homology, and known physiological responses of Fc receptors in addition to well phenotyped study populations for adequately powered association studies. Such studies have provided important insights into pathogenetic mechanisms and potential novel therapeutic approaches.

References

Salmon JE et al (1992) Allelic polymorphisms of human Fc gamma receptor IIA and Fc gamma receptor IIIb. Independent mechanisms for differences in human phagocyte function. J Clin Invest 89(4):1274–1281
Parren PW et al (1992) On the interaction of IgG subclasses with the low affinity Fc gamma RIIa (CD32) on human monocytes, neutrophils, and platelets. Analysis of a functional polymorphism to human IgG2. J Clin Invest 90(4):1537–1546
Bredius RG et al (1994a) Role of neutrophil Fc gamma RIIa (CD32) and Fc gamma RIIB (CD16) polymorphic forms in phagocytosis of human IgG1- and IgG3-opsonized bacteria and erythrocytes. Immunology 83(4):624–630

Maxwell KF et al (1999) Crystal structure of the human leukocyte Fc receptor, Fc gammaRIIa. Nat Struct Biol 6(5):437–442

Bredius RG et al (1993) Phagocytosis of Staphylococcus aureus and Haemophilus influenzae type B opsonized with polyclonal human IgG1 and IgG2 antibodies. Functional hFc gamma RIIA polymorphism to IgG2. J Immunol 151(3):1463–1472

International Consortium for Systemic Lupus Erythematosus, G., et al (2008) Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet. 40(2):204–10

Saruhan-Direskeneli G et al (2013) Identification of multiple genetic susceptibility loci in Takayasu arteritis. Am J Hum Genet 93(2):298–305

Raychaudhuri S et al (2009) Genetic variants at CD28, PRDM1 and CD2/CD58 are associated with rheumatoid arthritis risk. Nat Genet 41(12):1313–1318

McGovern DP et al (2010) Genome-wide association identifies multiple ulcerative colitis susceptibility loci. Nat Genet 42(4):332–337

Asano K et al (2009) A genome-wide association study identifies three new susceptibility loci for ulcerative colitis in the Japanese population. Nat Genet 41(12):1325–1329

Lessard CJ et al (2013) Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjogren’s syndrome. Nat Genet 45(11):1284–1292

Kettunen J et al (2012) Genome-wide association study identifies multiple loci influencing human serum metabolite levels. Nat Genet 44(3):269–276

Kyogoku C et al (2002a) Fcgamma receptor gene polymorphisms in Japanese patients with systemic lupus erythematosus: contribution of FCGR2B to genetic susceptibility. Arthritis Rheum 46(5):1242–1254

Li X et al (2003) A novel polymorphism in the Fcgamma receptor IIB (CD32B) transmembrane region alters receptor signaling. Arthritis Rheum 48(11):3242–3252

Kono H et al (2005) FcgammaRIIB Ile232Thr transmembrane polymorphism associated with human systemic lupus erythematosus decreases affinity to lipid rafts and attenuates inhibitory effects on B cell receptor signaling. Hum Mol Genet 14(19):2881–2892

Floto RA et al (2005) Loss of function of a lupus-associated FcgammaRIIb polymorphism through exclusion from lipid rafts. Nat Med 11(10):1056–1058

Su K et al (2004a) A promoter haplotype of the immunoreceptor tyrosine-based inhibitory motif-bearing FcgammaRIIb alters receptor expression and associates with autoimmunity. I. Regulatory FCGR2B polymorphisms and their association with systemic lupus erythematosus. J Immunol 172(11):7186–7191

Su K et al (2004b) A promoter haplotype of the immunoreceptor tyrosine-based inhibitory motif-bearing FcgammaRIIb alters receptor expression and associates with autoimmunity. II. Differential binding of GATA4 and Yin-Yang1 transcription factors and correlated receptor expression and function. J Immunol 172(11):7192–7199

Blank MC et al (2005) Decreased transcription of the human FCGR2B gene mediated by the -343 G/C promoter polymorphism and association with systemic lupus erythematosus. Hum Genet 117(2–3):220–227

Metes D et al (1999) Ligand binding specificities and signal transduction pathways of Fc gamma receptor IIC isoforms: the CD32 isoforms expressed by human NK cells. Eur J Immunol 29(9):2842–2852

Stewart-Akers AM et al (2004) Fc gamma R expression on NK cells influences disease severity in rheumatoid arthritis. Genes Immun 5(7):521–529

Metes D et al (1998) Expression of functional CD32 molecules on human NK cells is determined by an allelic polymorphism of the FcgammaRIIC gene. Blood 91(7):2369–2380

Li X et al (2013) Allelic-dependent expression of an activating fc receptor on B cells enhances humoral immune responses. Sci Transl Med 5(216):216ra175
Ernst LK et al (2002) Allelic polymorphisms in the FcgammaRIIC gene can influence its function on normal human natural killer cells. J Mol Med (Berl) 80(4):248–257

Breunis WB et al (2008) Copy number variation of the activating FCGR2C gene predisposes to idiopathic thrombocytopenic purpura. Blood 111(3):1029–1038

Wu J et al (1997) A novel polymorphism of FcgammaRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. J Clin Invest 100(5):1059–1070

Koene HR et al (1997) Fc gammaRIIIa-158 V/F polymorphism influences the binding of IgG by natural killer cell Fc gammaRIIIa, independently of the Fc gammaRIIIa-48L/R/H phenotype. Blood 90(3):1109–1114

Ravetch JV, Perussia B (1989) Alternative membrane forms of Fc gamma RIII(CD16) on human natural killer cells and neutrophils. Cell type-specific expression of two genes that differ in single nucleotide substitutions. J Exp Med 170(2):481–497

Salmon JE, Edberg JC, Kimberly RP (1990) Fc gamma receptor III on human neutrophils. Allelic variants have functionally distinct capacities. J Clin Invest 85(4):1287–1295

Bux J et al (1997) Characterization of a new alloantigen (SH) on the human neutrophil Fc gamma receptor IIIb. Blood 89(3):1027–1034

Jasek M et al (2004) A novel polymorphism in the cytoplasmic region of the human immunoglobulin A Fe receptor gene. Eur J Immunogenet 31(2):59–62

Wu J et al (2007) FcalphaRI (CD89) alleles determine the proinflammatory potential of serum IgA. J Immunol 178(6):3973–3982

Shikanai T et al (1985, 2002) Sequence variants in the Fc epsilonRI alpha chain gene. J Appl Physiol 93(1):37–41

Hasegawa M et al (2003) A novel -66T/C polymorphism in Fc epsilon RI alpha-chain promoter affecting the transcription activity: possible relationship to allergic diseases. J Immunol 171(4):1927–1933

Potaczel DP et al (2006) The alpha-chain of high-affinity receptor for IgE (Fc epsilonRIalpha) gene polymorphisms and serum IgE levels. Allergy 61(10):1230–1233

Nishiya C (2006) Molecular mechanism of allergy-related gene regulation and hematopoietic cell development by transcription factors. Biosci Biotechnol Biochem 70(1):1–9

Kim SH et al (2006a) Genetic mechanism of aspirin-induced urticaria/angioedema. Curr Opin Allergy Clin Immunol 6(4):266–270

Bae JS et al (2007) Significant association of Fc epsilonRI alpha promoter polymorphisms with aspirin-intolerant chronic urticaria. J Allergy Clin Immunol 119(2):449–456

Kanada S et al (2008) Two different transcription factors discriminate the -315C > T polymorphism of the Fc epsilon RI alpha gene: binding of Sp1 to -315C and of a high mobility group-related molecule to -315T. J Immunol 180(12):8204–8210

Wu J et al (2002) Conservation of Fc epsilonRI gamma chain coding region in normals and in SLE patients. Lupus 11(1):42–45

Nishiya C et al (2004) Polymorphisms in the Fc epsilon RI beta promoter region affecting transcription activity: a possible promoter-dependent mechanism for association between Fc epsilon RI beta and atopy. J Immunol 173(10):6458–6464

Meng JF, McFall C, Rosenwasser LJ (2007) Polymorphism R62 W results in resistance of CD23 to enzymatic cleavage in cultured cells. Genes Immun 8(3):215–223

Liu YJ et al (1991) Recombinant 25-kDa CD23 and interleukin 1 alpha promote the survival of germinal center B cells: evidence for bifurcation in the development of centrocytes rescued from apoptosis. Eur J Immunol 21(5):1107–1114

Chan MA et al (2014) FCER2 (CD23) Asthma-Related Single Nucleotide Polymorphisms Yields Increased IgE Binding and Egr-1 Expression in Human B Cells. Am J Respir Cell Mol Biol 50(2):263–269

Davis RS et al (2002) Fc receptor homologs: newest members of a remarkably diverse Fc receptor gene family. Immunol Rev 190:123–136

Kochi Y et al (2005) A functional variant in FCRL3, encoding Fc receptor-like 3, is associated with rheumatoid arthritis and several autoimmune diseases. Nat Genet 37(5):478–485
Gibson AW et al (2009) The FCRL3-169CT promoter single-nucleotide polymorphism, which is associated with systemic lupus erythematosus in a Japanese population, predicts expression of receptor protein on CD19 + B cells. Arthritis Rheum 60(11):3510–3512
Chu X et al (2011) A genome-wide association study identifies two new risk loci for Graves’ disease. Nat Genet 43(9):897–901
Chistiakov DA, Chistiakov AP (2007) Is FCRL3 a new general autoimmunity gene? Hum Immunol 68(5):375–383
Sachs UJ et al (2006) A variable number of tandem repeats polymorphism influences the transcriptional activity of the neonatal Fc receptor alpha-chain promoter. Immunology 119(1):83–89
Clark MR et al (1990) An abnormality of the gene that encodes neutrophil Fc receptor III in a patient with systemic lupus erythematosus. J Clin Invest 86(1):341–346
Huizinga TW et al (1990) Maternal genomic neutrophil FcRIII deficiency leading to neonatal isoimmune neutropenia. Blood 76(10):1927–1932
Koene HR et al (1998a) Fc gamma RIIIB gene duplication: evidence for presence and expression of three distinct Fc gamma RIIIB genes in NA(1 + ,2 + )SH(+) individuals. Blood 91(2):673–679
Willcocks LC et al (2008) Copy number of FCGR3B, which is associated with systemic lupus erythematosus, correlates with protein expression and immune complex uptake. J Exp Med 205(7):1573–1582
de Haas M et al (1995) Neutrophil Fc gamma RIIib deficiency, nature, and clinical consequences: a study of 21 individuals from 14 families. Blood 86(6):2403–2413
Reilly AF et al (1994) Variation in human FCGR2C gene copy number. Immunogenetics 40(6):456
Breunis WB et al (2009) Copy number variation at the FCGR locus includes FCGR3A, FCGR2C and FCGR3B but not FCGR2A and FCGR2B. Hum Mutat 30(5):E640–E650
Li X et al (2009) Fcgamma receptors: structure, function and role as genetic risk factors in SLE. Genes Immun 10(5):380–389
Jeffers R, Kumararatne DS (1990) Selective IgG subclass deficiency: quantification and clinical relevance. Clin Exp Immunol 81(3):357–367
Endeman H et al (2009) The Fc gamma receptor IIa-R/R131 genotype is associated with severe sepsis in community-acquired pneumonia. Clin Vaccine Immunol 16(7):1087–1090
Platonov AE et al (1998) Association of human Fc gamma RIa (CD32) polymorphism with susceptibility to and severity of meningococcal disease. Clin Infect Dis 27(4):746–750
Jansen WT et al (1999) Fc gamma receptor polymorphisms determine the magnitude of in vitro phagocytosis of Streptococcus pneumoniae mediated by pneumococcal conjugate sera. J Infect Dis 180(3):888–891
Yee AM et al (2000) Association between FcgammaRIIa-R131 allotype and bacteremic pneumococcal pneumonia. Clin Infect Dis 30(1):25–28
Sanders LA et al (1994) Fc gamma receptor IIa (CD32) heterogeneity in patients with recurrent bacterial respiratory tract infections. J Infect Dis 170(4):854–861
Bredius RG et al (1994b) Fc gamma receptor IIa (CD32) polymorphism in fulminant meningococcal septic shock in children. J Infect Dis 170(4):848–853
Yuan FF et al (2005) Influence of FcgammaRIIa and MBL polymorphisms on severe acute respiratory syndrome. Tissue Antigens 66(4):291–296
Stein MP et al (2000) C-reactive protein binding to FcgammaRIIa on human monocytes and neutrophils is allele-specific. J Clin Invest 105(3):369–376
Weiser JN et al (1998) Phosphorylcholine on the lipopolysaccharide of Haemophilus influenzae contributes to persistence in the respiratory tract and sensitivity to serum killing mediated by C-reactive protein. J Exp Med 187(4):631–640
Yuan ZN et al (1999) Topical distribution of Fc gammaRI, Fc gammaRII and Fc gammaRIII in inflamed human gingiva. J Clin Periodontol 26(7):441–447
Nicu EA et al (2007) Hyper-reactive PMNs in FcgammaRIIa 131 H/H genotype periodontitis patients. J Clin Periodontol 34(11):938–945
Kobayashi T et al (2000) Relevance of IgG receptor IIb (CD16) polymorphism to handling of Porphyromonas gingivalis: implications for the pathogenesis of adult periodontitis. J Periodontal Res 35(2):65–73

Song GG, Lee YH (2013) Associations between FCGR2A rs1801274, FCGR3A rs396991, FCGR3B NA1/NA2 polymorphisms and periodontitis: a meta-analysis. Mol Biol Rep 40(8):4985–4993

Yasuda K et al (2003) FcgammaRIIB gene polymorphisms in Japanese periodontitis patients. Genes Immun 4(8):541–546

Horino K et al (1989) Effects of anti-Bacteroides gingivalis (Bg), and anti-Actinobacillus actinomycetemcomitans (Aa) antibodies on Bg and Aa. Nihon Shishubyo Gakkai Kaishi 31(1):1–12

Sugita N et al (2012) Association of the FcgammaRIIB-nt645 + 25A/G polymorphism with the expression level of the FcgammaRIIb receptor, the antibody response to Porphyromonas gingivalis and the severity of periodontitis. J Periodontal Res 47(1):105–113

Chai L et al (2010) SNPs of Fc-gamma receptor genes and chronic periodontitis. J Dent Res 89(7):705–710

Moi ML et al (2010) Involvement of the Fc gamma receptor IIA cytoplasmic domain in antibody-dependent enhancement of dengue virus infection. J Gen Virol 91(1):103–111

Littaua R, Kurane I, Ennis FA (1990) Human IgG Fc receptor II mediates antibody-dependent enhancement of dengue virus infection. J Immunol 144(8):3183–3186

Garcia G et al (2011) Long-term persistence of clinical symptoms in dengue-infected persons and its association with immunological disorders. Int J Infect Dis 15(1):e38–e43

Loke H et al (2002) Susceptibility to dengue hemorrhagic fever in vietnam: evidence of an association with variation in the vitamin d receptor and Fc gamma receptor IIa genes. Am J Trop Med Hyg 67(1):102–106

Garcia G et al (2010) Asymptomatic dengue infection in a Cuban population confirms the protective role of the RR variant of the FcgammaRIIa polymorphism. Am J Trop Med Hyg 82(6):1153–1156

Zuniga J et al (2012) Genetic variants associated with severe pneumonia in A/H1N1 influenza infection. Eur Respir J 39(3):604–610

Diamantopoulos PT et al (2013) Correlation of Fc-gamma RIIA polymorphisms with latent Epstein-Barr virus infection and latent membrane protein 1 expression in patients with low grade B-cell lymphomas. Leuk Lymphoma 54(9):2030–2034

Forthal DN et al (2007) FcgammaRIIA genotype predicts progression of HIV infection. J Immunol 179(11):7916–7923

Lehrnbecher TL et al (2000) Variant genotypes of FcgammaRIIIA influence the development of Kaposi’s sarcoma in HIV-infected men. Blood 95(7):2386–2390

Nolle B et al (1989) Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. Ann Intern Med 111(1):28–40

Ralston DR et al (1997) Antineutrophil cytoplasmic antibodies induce monocyte IL-8 release. Role of surface proteinase-3, alpha1-antitrypsin, and Fcgamma receptors. J Clin Invest 100(6):1416–1424

Porges AJ et al (1994) Anti-neutrophil cytoplasmic antibodies engage and activate human neutrophils via Fc gamma RIIs. J Immunol 153(3):1271–1280

Kessenbrock K et al (2009) Netting neutrophils in autoimmune small- vessel vasculitis. Nat Med 15(6):623–625

Sangaletti S et al (2012) Neutrophil extracellular traps mediate transfer of cytoplasmic neutrophil antigens to myeloid dendritic cells toward ANCA induction and associated autoimmunity. Blood 120(15):3007–3018

Edberg JC et al (1997) Analysis of FcgammaRII gene polymorphisms in Wegner’s granulomatosis. Exp Clin Immunogenet 14(3):183–195

Tse WY et al (2000) Neutrophil FcgammaRIIhb allelic polymorphism in anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis. Clin Exp Immunol 119(3):574–577
Tse WY et al (1999) No association between neutrophil FcgammaRIIa allelic polymorphism and anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis. Clin Exp Immunol 117(1):198–205
Kocher M et al (1998) Antineutrophil cytoplasmic antibodies preferentially engage Fc gammaRIIb on human neutrophils. J Immunol 161(12):6909–6914
Fanciulli M et al (2007) FCGR3B copy number variation is associated with susceptibility to systemic, but not organ-specific, autoimmunity. Nat Genet 39(6):721–723
Neira O et al (1996) Lyme disease in Chile. Prevalence study in selected groups. Rev Med Chil 124(5):537–544
Kelley JM et al (2011) IgA and IgG antineutrophil cytoplasmic antibody engagement of Fc receptor genetic variants influences granulomatosis with polyangiitis. Proc Natl Acad Sci U S A 108(51):20736–20741
Shrestha S et al (2012) Role of activating FcgammaR gene polymorphisms in Kawasaki disease susceptibility and intravascular immunoglobulin response. Circ Cardiovasc Genet 5(3):309–316
Onouchi Y et al (2012) A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet 44(5):517–521
Taniuchi S et al (2005) Polymorphism of Fc gamma RIIa may affect the efficacy of gammaglobulin in Kawasaki disease. J Clin Immunol 25(4):309–313
Breunis WBH, Long T, Eileen Png, Geissler J, Nagelkerke S, Ellis J, Davila S, Chiea Chuen K, Levin M, Burgner D, Shimizu C, Burns JC., Hibberd ML, Kuipers TW (2013) Fc-Gamma Receptor Genetic Variation In Kawasaki Disease. In: American college of rheumatology2013, San Diego
Asano K et al (2013) Impact of allele copy number of polymorphisms in FCGR3A and FCGR3B genes on susceptibility to ulcerative colitis. Inflamm Bowel Dis 19(10):2061–2068
Harley IT et al (2009) Genetic susceptibility to SLE: new insights from fine mapping and genome-wide association studies. Nat Rev Genet 10(5):285–290
Salmon JE et al (1996) Fc gamma RIIA alleles are heritable risk factors for lupus nephritis in African Americans. J Clin Invest 97(5):1348–1354
Edberg JC et al (2002) Genetic linkage and association of Fcgamma receptor IIIA (CD16A) on chromosome 1q23 with human systemic lupus erythematosus. Arthritis Rheum 46(8):2132–2140
Manger K et al (2002) Fcgamma receptor IIa, IIIa, and IIIb polymorphisms in German patients with systemic lupus erythematosus: association with clinical symptoms. Ann Rheum Dis 61(9):786–792
Karassa FB et al (2002) Role of the Fcgamma receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. Arthritis Rheum 46(6):1563–1571
Magnusson V et al (2004) Polymorphisms of the Fc gamma receptor type IIb gene are not associated with systemic lupus erythematosus in the Swedish population. Arthritis Rheum 50(4):1348–1350
Kyogoku C et al (2004) Association of Fcgamma receptor IIa, but not IIb and IIIa, polymorphisms with systemic lupus erythematosus: A family-based association study in Caucasians. Arthritis Rheum 50(2):671–673
Siriboonrit U et al (2003) Association of Fcgamma receptor IIb and IIIb polymorphisms with susceptibility to systemic lupus erythematosus in Thais. Tissue Antigens 61(5):374–383
Lee EB et al (2002) Fcgamma receptor IIIA polymorphism in Korean patients with systemic lupus erythematosus. Rheumatol Int 21(6):222–226
Chu ZT et al (2004) Association of Fcgamma receptor IIb polymorphism with susceptibility to systemic lupus erythematosus in Chinese: a common susceptibility gene in the Asian populations. Tissue Antigens 63(1):21–27
Weersma RK et al (2010) Association of FcgR2a, but not FcgR3a, with inflammatory bowel diseases across three Caucasian populations. Inflamm Bowel Dis 16(12):2080–2089
van der Pol WL et al (2003) Association of the Fc gamma receptor IIA-R/R131 genotype with myasthenia gravis in Dutch patients. J Neuroimmunol 144(1–2):143–147
Zhou X J et al (2010a) FCGR2B gene polymorphism rather than FCGR2A, FCGR3A and FCGR3B is associated with anti-GBM disease in Chinese. Nephrol Dial Transplant 25(1): 97–101
Jonsen A et al (2007) Association between SLE nephritis and polymorphic variants of the CRP and FegammaRIIIa genes. Rheumatology (Oxford) 46(9):1417–1421
Dong C et al (2013) FgammaRIIIa SNPs and haplotypes affect human IgG binding and association with lupus nephritis in African Americans. Arthritis Rheum, doi: 10.1002/art. 38337
Koene HR et al (1998b) The Fc gammaRIIIA-158F allele is a risk factor for systemic lupus erythematosus. Arthritis Rheum 41(10):1813–1818
Kyogoku C et al (2002b) Studies on the association of Fc gamma receptor IIA, IIB, IIIA and IIIB polymorphisms with rheumatoid arthritis in the Japanese: evidence for a genetic interaction between HLA-DRB1 and FCGR3A. Genes Immun 3(8):488–493
Alarcon GS et al (2006) Time to renal disease and end-stage renal disease in PROFILE: a multiethnic lupus cohort. PLoS Med 3(10):e396
Hatta Y et al (1999) Association of Fc gamma receptor IIIB, but not of Fc gamma receptor IIA and IIIA polymorphisms with systemic lupus erythematosus in Japanese. Genes Immun 1(1):53–60
Gonzalez-Escribano MF et al (2002) FegammaRIIA, FegammaRIIIA and FegammaRIIB polymorphisms in Spanish patients with systemic lupus erythematosus. Eur J Immunogenet 29(4):301–306
You Y et al (2008) Lack of association between Fc receptor-like 3 gene polymorphisms and systemic lupus erythematosus in Chinese population. J Dermatol Sci 52(2):118–122
Choi CB et al (2006) The -169C/T polymorphism in FCRL3 is not associated with susceptibility to rheumatoid arthritis or systemic lupus erythematosus in a case-control study of Koreans. Arthritis Rheum 54(12):3838–3841
Ramirez-Bello J et al (2013) Juvenile rheumatoid arthritis and asthma, but not childhood-onset systemic lupus erythematosus are associated with FCRL3 polymorphisms in Mexicans. Mol Immunol 53(4):374–378
Piotrowski P et al (2013) The FCRL3 -169T > C polymorphism might be associated with some autoantibody presence in patients with SLE in a Polish population. Mod Rheumatol 24(2):296–299
Mao C et al (2010) Association between Fc receptor-like 3 C169T polymorphism and risk of systemic lupus erythematosus: a meta-analysis. Mol Biol Rep 37(1):191–196
Song GG et al (2013) Fc receptor-like 3 (FCRL3) -169 C/T polymorphism and systemic lupus erythematosus: a meta-analysis. Rheumatol Int 33(9):2323–2329
Morgan AW et al (2000) Fegamma receptor type IIIA is associated with rheumatoid arthritis in two distinct ethnic groups. Arthritis Rheum 43(10):2328–2334
Morgan AW et al (2003) FegammaRIIIA-158 V and rheumatoid arthritis: a confirmation study. Rheumatology (Oxford) 42(4):528–533
Thabet MM et al (2007) FCRL3 promoter 169 CC homozygosity is associated with susceptibility to rheumatoid arthritis in Dutch Caucasians. Ann Rheum Dis 66(6):803–806
Eike MC et al (2008) The FCRL3 -169T > C polymorphism is associated with rheumatoid arthritis and shows suggestive evidence of involvement with juvenile idiopathic arthritis in a Scandinavian panel of autoimmune diseases. Ann Rheum Dis 67(9):1287–1291
Maehlen MT et al (2011) FCRL3 -169C/C genotype is associated with anti-citrullinated protein antibody-positive rheumatoid arthritis and with radiographic progression. J Rheumatol 38(11):2329–2335
Wu H et al (2010) Fc receptor-like 3 gene polymorphisms confer susceptibility to rheumatoid arthritis in a Chinese population. Hum Immunol 71(12):1203–1208
Bajpai UD et al (2012) A functional variant in FCRL3 is associated with higher Fc receptor-like 3 expression on T cell subsets and rheumatoid arthritis disease activity. Arthritis Rheum 64(8):2451–2459
Han SW et al (2012) FCRL3 gene polymorphisms contribute to the radiographic severity rather than susceptibility of rheumatoid arthritis. Hum Immunol 73(5):537–542
Zeng Z et al (2012) Association of FCRL4 polymorphisms on disease susceptibility and severity of ankylosing spondylitis in Chinese Han population. Clin Rheumatol 31(10):1449–1454
Tang X et al (2009) A single-nucleotide polymorphism marker within the FCRL5 gene and HLA-B27 positive Han Chinese ankylosing spondylitis patients. Tissue Antigens 74(4):314–316
Owen CJ et al (2007) Analysis of the Fc receptor-like-3 (FCRL3) locus in Caucasians with autoimmune disorders suggests a complex pattern of disease association. J Clin Endocrinol Metab 92(3):1106–1111
Duchatelet S et al (2008) FCRL3 -169CT functional polymorphism in type 1 diabetes and autoimmunity traits. Biomed Pharmacother 62(3):153–157
Inoue N et al (2012) Associations between autoimmune thyroid disease prognosis and functional polymorphisms of susceptibility genes, CTLA4, PTPN22, CD40, FCRL3, and ZFAT, previously revealed in genome-wide association studies. J Clin Immunol 32(6):1243–1252
Gu LQ et al (2010) Clinical associations of the genetic variants of CTLA-4, Tg, TSHR, PTPN22, PTPN12 and FCRL3 in patients with Graves’ disease. Clin Endocrinol (Oxf) 72(2):248–255
Plagnol V et al (2011) Genome-wide association analysis of autoantibody positivity in type 1 diabetes cases. PLoS Genet 7(8):e1002216
Howson JM et al (2012) Genetic association of zinc transporter 8 (ZnT8) autoantibodies in type 1 diabetes cases. Diabetologia 55(7):1978–1984
Martinez A et al (2007a) FcRL3 and multiple sclerosis pathogenesis: role in autoimmunity? J Neuroimmunol 189(1–2):132–136
Matesanz F et al (2008) The high producer variant of the Fc-receptor like-3 (FCRL3) gene is involved in protection against multiple sclerosis. J Neuroimmunol 195(1–2):146–150
Martinez A et al (2007b) Epistatic interaction between FCRL3 and MHC in Spanish patients with IBD. Tissue Antigens 69(4):313–317
Zhou J et al (2012) Association of polymorphisms in the promoter region of FCER1A gene with atopic dermatitis, chronic urticaria, asthma, and serum immunoglobulin E levels in a Han Chinese population. Hum Immunol 73(3):301–305
Niwa Y et al (2010) FcEpsilonRIalpha gene (FCER1A) promoter polymorphisms and total serum IgE levels in Japanese atopic dermatitis patients. Int J Immunogenet 37(2):139–141
Weidinger S et al (2008) Genome-wide scan on total serum IgE levels identifies FCER1A as a novel susceptibility locus. PLoS Genet 4(8):e1000166
Granada M et al (2012) A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study. J Allergy Clin Immunol 129(3):840–845 e21
MacGlashan D Jr (2005) IgE and FcEpsilonRI regulation. Clin Rev Allergy Immunol 29(1):49–60
Kim YK et al (2007) Association and functional relevance of E237G, a polymorphism of the high-affinity immunoglobulin E-receptor beta chain gene, to airway hyper-responsiveness. Clin Exp Allergy 37(4):592–598
Zhang X et al (2004) The E237G polymorphism of the high-affinity IgE receptor beta chain and asthma. Ann Allergy Asthma Immunol 93(5):499–503
Laprise C et al (2000) Evidence for association and linkage between atopy, airway hyper-responsiveness, and the beta subunit Glu237Gly variant of the high-affinity receptor for immunoglobulin E in the French-Canadian population. Immunogenetics 51(8–9):695–702
Nagata H et al (2001) Association between nasal allergy and a coding variant of the Fc epsilon RI beta gene Glu237Gly in a Japanese population. Hum Genet 109(3):262–266
Li A, Hopkin JM (1997) Atopy phenotype in subjects with variants of the beta subunit of the high affinity IgE receptor. Thorax 52(7):654–655
Hizawa N et al (2000) A common FCER1B gene promoter polymorphism influences total serum IgE levels in a Japanese population. Am J Respir Crit Care Med 161(3 Pt 1):906–909
Kim SH et al (2006b) A polymorphism of MS4A2 (-109T > C) encoding the beta-chain of the high-affinity immunoglobulin E receptor (FcepsilonR1beta) is associated with a susceptibility to aspirin-intolerant asthma. Clin Exp Allergy 36(7):877–883
Yang HJ et al (2014) Association of the MS4A2 gene promoter C-109T or the 7th exon E237G polymorphisms with asthma risk: A meta-analysis. Clin Biochem 47(7-8):605–611
Laitinen T et al (2000) Association study of the chromosomal region containing the FCER2 gene suggests it has a regulatory role in atopic disorders. Am J Respir Crit Care Med 161(3 Pt 1):700–706
Koster ES et al (2011) FCER2 T2206C variant associated with chronic symptoms and exacerbations in steroid-treated asthmatic children. Allergy 66(12):1546–1552
Tantisira KG et al (2007) FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. J Allergy Clin Immunol 120(6):1285–1291
Sharma V et al (2014) A role of FCER1A and FCER2 polymorphisms in IgE regulation. Allergy 69(2):231–236
Potaczek DP et al (2009) Interaction of functional FCER2 promoter polymorphism and phenotype-associated haplotypes. Tissue Antigens 74(6):534–538
Kaneko M et al (1995) Allergen-specific IgG1 and IgG3 through Fc gamma RII induce eosinophil degranulation. J Clin Invest 95(6):2813–2821
Jonsson F et al (2012) Human FcgammaRIIA induces anaphylactic and allergic reactions. Blood 119(11):2533–2544
Williams JW, Tjota MY, Sperling AI (2012) The contribution of allergen-specific IgG to the development of th2-mediated airway inflammation. J Allergy (Cairo) 2012:236075
Lau S et al (2005) Longitudinal study on the relationship between cat allergen and endotoxin exposure, sensitization, cat-specific IgG and development of asthma in childhood–report of the German Multicentre Allergy Study (MAS 90). Allergy 60(6):766–773
Bruhns P, Fremont S, Daeron M (2005) Regulation of allergy by Fc receptors. Curr Opin Immunol 17(6):662–669
Wu et al (2014) Functional Fc gamma receptor polymorphisms are associated with human allergy. PLOS one 9(2):e89196
Robledo G et al (2012) Association of the FCGR3A-158F/V gene polymorphism with the response to rituximab treatment in Spanish systemic autoimmune disease patients. DNA Cell Biol 31(12):1671–1677
Cooper N et al (2012) Platelet-associated antibodies, cellular immunity and FCGR3a genotype influence the response to rituximab in immune thrombocytopenia. Br J Haematol 158(4):539–547
Dijstelbloem HM et al (1999) Fcgamma receptor polymorphisms in Wegener’s granulomatosis: risk factors for disease relapse. Arthritis Rheum 42(9):1823–1827
Norworthy P et al (1999) Overrepresentation of the Fcgamma receptor type IIa R131/R131 genotype in caucasoid systemic lupus erythematosus patients with autoantibodies to C1q and glomerulonephritis. Arthritis Rheum 42(9):1828–1832
Song YW et al (1998) Abnormal distribution of Fc gamma receptor type IIa polymorphisms in Korean patients with systemic lupus erythematosus. Arthritis Rheum 41(3):421–426
Dijstelbloem HM et al (2000) Fcgamma receptor polymorphisms in systemic lupus erythematosus: association with disease and in vivo clearance of immune complexes. Arthritis Rheum 43(12):2793–2800
Morgan AW et al (2006a) Association of FCGR2A and FCGR2A-FCGR3A haplotypes with susceptibility to giant cell arteritis. Arthritis Res Ther 8(4):R109
van der Pol WL et al (2000) IgG receptor IIa alleles determine susceptibility and severity of Guillain-Barre syndrome. Neurology 54(8):1661–1665
Khor CC et al (2011) Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. Nat Genet 43(12):1241–1246
Orru V et al (2013) Genetic variants regulating immune cell levels in health and disease. Cell 155(1):242–256
Chen JY et al (2006) Association of a transmembrane polymorphism of Fcgamma receptor IIb (FCGR2B) with systemic lupus erythematosus in Taiwanese patients. Arthritis Rheum 54(12):3908–3917
Olferiev M et al (2007) The role of activating protein 1 in the transcriptional regulation of the human FCGR2B promoter mediated by the -343 G -> C polymorphism associated with systemic lupus erythematosus. J Biol Chem 282(3):1738–1746
Morgan AW et al (2006b) Analysis of Fcgamma receptor haplotypes in rheumatoid arthritis: FCGR3A remains a major susceptibility gene at this locus, with an additional contribution from FCGR3B. Arthritis Res Ther 8(1):R5
Zhou XJ et al (2010b) Copy number variation of FCGR3A rather than FCGR3B and FCGR2B is associated with susceptibility to anti-GBM disease. Int Immunol 22(1):45–51
Foster CB et al (2001) Polymorphisms in inflammatory cytokines and Fcgamma receptors in childhood chronic immune thrombocytopenic purpura: a pilot study. Br J Haematol 113(3):596–599
Niederer HA et al (2010) Copy number, linkage disequilibrium and disease association in the FCGR locus. Hum Mol Genet 19(16):3282–3294
Nossent JC, Rischmueller M, Lester S (2012) Low copy number of the Fc-gamma receptor 3B gene FCGR3B is a risk factor for primary Sjogren’s syndrome. J Rheumatol 39(11):2142–2147
Osuga Y et al (2011) Lymphocytes in endometriosis. Am J Reprod Immunol 65(1):1–10
Teles JS et al (2011) Association of FCRL3 C-169T promoter single-nucleotide polymorphism with idiopathic infertility and infertility-related endometriosis. J Reprod Immunol 89(2):212–215
Szczepanska M et al (2013) The FCRL3 -169T > C polymorphism and the risk of endometriosis-related infertility in a Polish population. Arch Gynecol Obstet 288(4):799–804