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Human FcR Polymorphism and Disease

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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.

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 Part II and III. 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

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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 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 through put 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 extra-cellular 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 158 V 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-158 V (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 c-chain pairing, FcαR-S248 allele fails to induce pro-inflammatory cytokines. In contrast, FcαR-G248 maintains signaling capacity even without the FcRc, producing both IL-6 and TNFa. 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 haplo-type (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 FcγRIIIb 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 pneumonia*, *Hemophilus influenza*, 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 homo-zygous for the R131 allele (Yee et al. 2000). Similarly, the FcγRIIa-131R allele is associated with increased infection by *Hemophilus influenza* 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

FcγRIIa 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 proinflammatory 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 (Siriboonrit 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 (Siriboonrit 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 (Chistiakov and Chistiakov 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 reheumatoid arthritis is discussed in the next chapter.

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-876 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 b-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 allergenspecific 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 Part V, “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.

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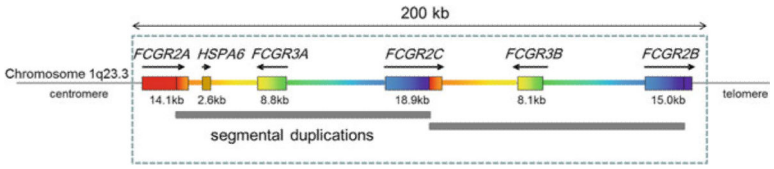

Fig. 1.

Genomic structure of the classical low-affinity FCGR cluster. Identical colors represent sequence homology. Figure adapted from Li et al. (2009)

Table 1

Genetic variations of classical FcγRs

Receptor	Genetic variation	Functional property	Disease/trait
FcγRIIa	R131H (rsl801274)	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)
	rsl0919543	increasing mRNA expression	TA (Saruhan-Direskeneli et al. 2013)
	27Q > W (rs9427397) (rs9427398)	unknown	KD (Breunis et al. 2013)
	rs58055840	unknown	Immunocyte levels (Orru et al. 2013)
	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)
FcγRUb	I232T (rsl050501)	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.l/2B.4[a] (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)
FcβRIIc	STP/Q13 (rsl0917661)	STP: pseudogene; Ql3 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)
FcγRIIIa	V158F rs396991	V158: higher affinity for IgGl, 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	Altered protein expression level	anti-GBM disease (Zhou et al. 2010)
	rs445509	unknown	Periodontitis (Chai et al. 2010)
FcγRIHb	NA1/NA2[b]	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)

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–glomerular basement membrane (anti-GBM) antibody disease; ANCA: anti neutrophil cytoplasmic antibodies

[a]Promoter haplotype. 2B.1: -120G-386T; 2B.4: -120C-386A

[b] Coding haplotype. NA1: 141G 147C 227A 349G; NA2: 141C 147T 227G 349A

Table 2

Genetic variations of FcεR, FcαR, FCRLs and FcRn

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)
FcsRI-P	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)
	–426C/T –654T/C	–426C and –654T:higher promoter activity/expression	atopy (Nishiyama et al. 2004)
FcsRII	R62 W (rs2228137)	W62:resistance to proteolytic cleavage	Asthma (Laitinen et al. 2000)
	rs3760687	unknown	High IgE (Sharma et al. 2014)
FcaRI	S248G	G248: higher IgA-mediated activation	SLE (Wu et al. 2007)
FCRL1	rs4971154	unknown	T1D (Plagnol 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)
	rsl4335	unknown	AS (Zeng et al. 2012)
	rs 10489674	unknown	AS (Zeng et al. 2012)
FCRL5	rsl2036228	unknown	AS (Tang et al. 2009)
	rs6427384	unknown	AS (Tang et al. 2009)
FcRn	VNTR[a]	altered promoter activity/expression	unknown

AD: atopic dermatitis; T1D: type-1 diabetes; AITD: autoimmune thyroid disease; MS: multiple sclerosis; GD: Graves' disease; AS: ankylosing spondylitis

[a]VNTR: variable number of tandem repeats