Ethnic variation of Fcγ receptor polymorphism in Sami and Norwegian populations

Øivind Torkildsen,[1] Egil Utsi,[2] Svein Ivar Mellgren,[3] Hanne F. Harbo,[4,5] Christian A. Vedeler[1] and Kjell-Morten Myhr[1]

[1]*The Multiple Sclerosis National Competence Centre, Haukeland University Hospital, Department of Clinical Medicine, Section for Neurology, University of Bergen,* [2]*Karasjok Heart Center, Karasjok,* [3]*Department of Neurology, University Hospital of North Norway, Tromsø,* [4]*Institute of Immunology, University of Oslo, Rikshospitalet and Rikshospitalet University Hospital and* [5]*Department of Neurology, Ullevål University Hospital, Oslo, Norway*

doi:10.1111/j.1365-2567.2005.02158.x
Received 7 January 2005; revised 11 February 2005; accepted 14 February 2005.
Correspondence: Dr Ø. Torkildsen, The Multiple Sclerosis National Competence Centre, Department of Neurology, Haukeland University Hospital, N-5021 Bergen, Norway. Email: oivind.torkildsen@gmail.no
Senior author: Øivind Torkildesen

Summary

Receptors for the Fc domain of IgG (FcγR) play a critical role in linking cellular and humoral immunity. The various FcγR genotypes may contribute to differences in infectious and immune-related diseases in various ethnic populations. The Samis are the aboriginal inhabitants of Norway and Fennoscandinavia and differ ethnically from the Norwegians. The distribution of various immune-related diseases has been reported to differ between Sami and Norwegians. This is the first study to evaluate the distribution of FcγR polymorphisms in a Sami population. Two hundred Samis were genotyped for polymorphisms in the FcγRIIA, FcγRIIIA and FcγRIIIB genes. The genotype and allele frequencies were compared with those of 272 healthy Norwegians. The Sami and Norwegian FcγRIIA, FcγRIIIA and FcγRIIIB genotypes differed significantly. The Samis had higher frequencies of the FcγRIIa-H/H131, FcγRIIIa-F/F158 and FcγRIIIb-NA1/NA1 genotypes. The FcγR genotypes were non-randomly distributed in both populations. These findings may be important for the prevalence of autoimmune and infectious diseases in the two populations.

Keywords: FcγR; immunoglobulin; ethnicity; autoimmunity; infectious disease

Introduction

Receptors for the Fc domain of immunoglobulin G (IgG, FcγR) play a critical role in linking cellular and humoral immunity. Binding of IgG to the FcγR can start a broad range of biological responses, including antibody-dependent cytotoxicity, endocytosis, phagocytosis, release of inflammatory mediators and augmentation of antigen presentation. In humans, eight genes clustered on the long arm of chromosome 1 (1q21–24) encode three classes of FcγR: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16).[1] Within each class, isoforms have been detected that vary in IgG binding capacity, molecular weight and distribution on the surface of haematopoietic cells. This heterogeneity is further enhanced by the genetic and functional polymorphisms of the three subclasses FcγRIIA, FcγRIIIA and FcγRIIIB. Several publications have reviewed the relevance of polymorphism in these FcγR subclasses for the susceptibility to and prognosis of autoimmune diseases.[2–4] These polymorphisms might also influence the susceptibility to and prognosis of infectious diseases,[5–8] biological responses to therapeutic agents[9,10] and the risk of allograft rejection.[11]

FcγRIIA, which is expressed on mononuclear phagocytes, neutrophils and platelets, has two codominantly expressed alleles, with histidine (H131) and arginine (R131), at extracellular amino acid position 131.[12] FcγRIIA-H131 exhibits higher affinity for human IgG3 and represents the only leukocyte FcγR capable of interaction with IgG2. Thus, FcγRIIAH/H-131 has a significantly higher affinity for IgG3 than FcγRIIAR/R-131, whereas FcγRIIAR/H-131 has an intermediate binding capacity. Further, phagocytes of the H/H genotype have a higher phagocytosis capability than H/R or R/R cells.[13]

FcγRIIIA, expressed on macrophages and natural killer cells, also has two codominantly expressed alleles, valine (V158) and phenylalanine (F158).[14,15] The FcγRV-158 allotype binds IgG1- and IgG3-containing immune

complexes more efficiently than FcγRF-158·[14] Finally, the gene coding for FcγRIIIB, exclusively expressed on neutrophils, bears the neutrophil antigen (NA) polymorphism. The two allotypes of FcγRIIIB NA1 and NA2 differ in at least five nucleotides, resulting in four different amino acids. FcγRIIIB-NA1 is more efficient in binding IgG1 and IgG3 immune complexes than FcγRIIIB-NA2.[13]

Several studies have found ethnic variation in distribution of the various FcγR genotypes.[16–19] The Samis in northern Norway are the aboriginal inhabitants of Norway and are ethnically different from the caucasoid Norwegians.[20] Studies have shown that the Sami and Norwegian populations differ in the distribution of immune-related diseases such as multiple sclerosis (MS),[21] atopic disease[22] and ankylosing spondylitis.[23] This study compared the distribution of the three FcγR-polymorphisms among 200 Samis and 272 Norwegian Caucasians.

Methods

Subjects

Blood samples from a total of 200 Samis (51% men and 49% women) with a mean age of 64·9 years (SD = 11·5) were collected consecutively at a medical specialist centre in Karasjok in northern Norway. All the Sami participants had parents and grandparents who spoke Sami natively and were thus considered to be of pure Sami heritage. No Sami participant had any immune-related disease such as MS, systemic lupus erythematosus, Sjögren's syndrome, diabetes mellitus, rheumatoid arthritis or other significant rheumatic disease. A total of 272 healthy Caucasians were included from western Norway as controls. The regional Ethics Committee approved the protocol, and informed consent was obtained from each individual.

Genotyping

Genomic DNA was extracted from whole blood with QIAamp^{TM} Blood Kit (Qiagen GmbH, Hilden, Germany) as described by the manufacturer. Each genotyping method was verified by sequencing of 10 patients, and each polymerase chain reaction (PCR) reaction was carried out with positive controls of each possible genotype.

FcγRIIA genotypes were determined using amplification refractory mutation system-PCR.[24] Briefly, the two allele specific primers EC2-131R/H (5′-CCA GAA TGG AAA ATC CCA GAA ATT CTC TC (G/A)-3′) in combination with the reverse primer TM1 (5′-CCA TTG GTG AAG AGC TGC CCA TGC TGG GCA-3′) were used to amplify a 980-bp fragment in separate PCR reactions. A 270 bp product amplified from the Tα22 gene served as an internal positive control. The PCR conditions were denaturation for 5 min at 94°, followed by 45 cycles of 94° for 45 s, 63° for 30 s and 72° for 90 s, and a final extension at 72° for 10 min.

FcγRIIIA was detected using a PCR-based method with Ampli Taq Stoffel enzyme as described previously.[25] Two PCR reactions were performed using allele specific primers for V/F: 5′-CTG AAG ACA CAT TTT TAC TCC CAA (C/A)-3′ and the reverse primer 5′-TCC AAA AGC CAC ACT CAA AGA C-3′). PCR conditions were denaturation for 5 min at 95°, followed by 35 cycles (94° for 30 s, 64° for 30 s and 72° for 30 s) and a final extension at 72° for 8 min.

FcγRIIIB was amplified using the NA1-specific primer (5′-CAG TGG TTT CAC AAT GTG AA-3′) and NA2-specific primer (5′-CAA TGG TAC AGC GTG CTT-3′) with the common reverse primer (5′-ATG GAC TTC TAG CTG CAC-3′) modified after Bux *et al.*[26] The 141 bp product for NA1 and 219 bp product for NA2 were amplified in the same reaction. A 439 bp product from the human growth hormone served as an internal positive control. PCR conditions were denaturation for 3 min at 94°, followed by 30 cycles of 94° for 1 min, 57° for 2 min and 72° for 1 min, and a final extension at 72° for 10 min.

All PCR products were analysed by electrophoresis, using 1·5% agarose gel with ethidium bromide and visualized by ultraviolet light.

Statistical analysis

Pearson's chi-square test was used for analysing the data. Statistical significance was defined as $P = 0{\cdot}05$. Bonferroni correction was performed, but this did not alter the significance of any of the results. Allele frequencies were compared using 2×2 tables containing the number of alleles in the study groups. Tests were performed on 3×3 tables to determine whether the genotypes on two loci were independent. The observed frequencies of FcγR combinations (FcγRIIA and FcγRIIIA, FcγRIIA and FcγRIIIB and FcγRIIIB and FcγRIIIA) were compared with the expected frequencies, assuming non-linked FcγR allele transmission using the method previously described by Van der Pol *et al.*[27] Finally, the triple homozygous frequencies and single heterozygous frequencies served to estimate the frequencies of FcγRIIA–FcγRIIIA–FcγRIIB allele combinations (FcγR haplotypes).[27] The analysis was performed with SPSS 11.0.

Results

Allele and genotype frequencies

The Samis and Norwegians differed in both genotype and allele frequencies of FcγRIIa. The Sami population had a higher frequency of the H/H genotype ($P < 0{\cdot}0001$) and higher frequency of the FcγRIIA-H131 allele (70%)

Table 1. Distibution of FcγR genotypes and alleles

FcγR	Sami population *n* (%)	Norwegian population *n* (%)	*P*-value
FcγRIIa			$P < 0{\cdot}0001$
H/H	94 (47·0)	56 (20·5)	
H/R	90 (45·0)	128 (47·0)	
R/R	16 (8·0)	88 (32·5)	
H	0·70	0·40	
R	0·30	0·60	$P < 0{\cdot}0001$
FcγRIIIa[1]			$P = 0{\cdot}0013$
V/V	9 (4·7)	37 (13·7)	
V/F	62 (32·1)	101 (37·4)	
F/F	122 (63·2)	132 (48·9)	
V	0·20	0·30	
F	0·80	0·70	$P < 0{\cdot}0001$
FcγRIII[2]			$P < 0{\cdot}0001$
NA1/1	52 (27·4)	34 (12·5)	
NA1/2	50 (26·3)	123 (45·2)	
NA2/2	88 (46·3)	115 (42·3)	
NA1	0·40	0·35	
NA2	0·60	0·65	$P = 0{\cdot}098$

[1]193 Samis participants were genotyped; [2]190 Samis participants were genotyped.

than the Norwegian population (40%) ($P < 0{\cdot}0001$) (Table 1). The distribution of the FcγRIIIA genotype also differed. The Sami population displayed a higher frequency of the F/F genotype ($P = 0{\cdot}0013$) and a higher frequency of the FcγRIIIA-F158 allele (80%) than the Norwegian controls (70%; $P < 0{\cdot}0001$) (Table 1). For FcγRIIIB, the Sami population had a higher frequency of the NA1/NA1 genotype ($P < 0{\cdot}0001$) and of the FcγRIIIb-NA1 allele (40%) than the Norwegian population (35%), although this failed to reach statistical significance ($P = 0{\cdot}098$; Table 1).

Distribution of FcγR genotype combinations

The observed and expected frequencies are for the Norwegian and Sami participants are summarized in Table 2. For the Samis, the frequencies of FcγRIIA–FcγRIIIA genotype combinations differed significantly from those assuming random transmission, with increased frequencies of FcγRIIA-R/R131–FcγRIIIA-F/F158 and FcγRIIA-H/H131–FcγRIIIA-V/V158 compared with FcγRIIA-R/R131–FcγRIIIA-V/V158 and FcγRIIA-H/H131–FcγRIIIA-F/F158, respectively ($\chi^2 = 12{\cdot}9$, $P = 0{\cdot}011$). The FcγRIIA-R/R13–FcγRIIIB-NA1/NA2 and FcγRIIA-H/H131–FcγRIIIB-NA1/NA1 frequencies were increased compared with FcγRIIA-R/R131–FcγRIIIB-NA1/NA1 and FcγRIIA-H/H131–FcγRIIIB-NA2/NA2 genotypes ($\chi^2 = 18{\cdot}7$, $P = 0{\cdot}001$). Finally, FcγRIIIB-NA1/NA1–FcγRIIIA-F/F158 and FcγRIIIB-NA2/NA2–FcγRIIIA-V/V158 frequencies were increased at the expense of FcγRIIIB-NA1/NA1–FcγRIIIA-V/V158 and FcγRIIIB-NA2/NA2–FcγRIIIA-F/F158 ($\chi^2 = 25{\cdot}3$, $P < 0{\cdot}001$).

Table 2. Absolute and expected numbers of combined FcγR genotypes

	Sami population		Norwegian population	
Genotype	Observed	Expected	Observed	Expected
FcγRIIa–FcγRIIIa				
RR/FF	14	10·2	8	12·1
RR/VF	2	5·2	26	32·9
RR/VV	0	0·7	54	43·0
HR/FF	55	54·0	11	17·4
HR/VF	30	27·4	55	47·5
HR/VV	0	3·5	61	62·1
HH/FF	53	57·8	18	7·5
HH/VF	30	29·4	20	20·6
HH/VV	8	3·8	17	26·9
	$\chi = 12{\cdot}936$; $P = 0{\cdot}011$		$\chi = 27{\cdot}356$; $P < 0{\cdot}001$	
FcγRIIa–FcγRIIIb				
RR/NA1/1	0	4·4	8	11·0
RR/NA1/2	10	4·2	33	39·8
RR/NA2/2	6	7·4	47	37·2
HR/NA1/1	20	24·2	20	16·0
HR/NA1/2	24	23·3	63	57·9
HR/NA2/2	44	40·5	45	54·1
HH/NA1/1	32	23·4	6	7·0
HH/NA1/2	16	22·5	27	25·3
HH/NA2/2	37	39·1	23	23·7
	$\chi = 18{\cdot}728$; $P = 0{\cdot}001$		$\chi = 7{\cdot}818$; $P = 0{\cdot}1$	
FcγRIIIb–FcγRIIIa				
NA1/1/FF	45	31·4	1	4·7
NA1/1/VF	6	17·1	12	12·7
NA1/1/VV	0	2·5	21	16·6
NA1/2/FF	28	30·2	12	16·9
NA1/2/VF	20	16·4	44	46·0
NA1/2/VV	1	2·4	67	60·1
NA2/2/FF	41	52·4	24	15·5
NA2/2/VF	36	28·5	45	42·3
NA2/2/VV	8	4·1	44	55·2
	$\chi = 25{\cdot}350$; $P < 0{\cdot}001$		$\chi = 13{\cdot}485$; $P = 0{\cdot}008$	

For the 272 Caucasian Norwegians, the frequencies of FcγRIIA–FcγRIIIA genotype combinations were significantly different from those assuming random transmission, with increased frequencies of FcγRIIA-R/R131–FcγRIIIA-V/V158 and FcγRIIA-H/H131–FcγRIIIA-F/F158 compared with FcγRIIA-R/R131–FcγRIIIA-F/F158 and FcγRIIA-H/H131–FcγRIIIA-V/V158, respectively ($\chi^2 = 27{\cdot}4$, $P < 0{\cdot}001$). The FcγRIIA–FcγRIIIB genotype combinations did not differ statistically from expected frequencies ($\chi^2 = 7{\cdot}8$, $P = 0{\cdot}1$). Finally, FcγRIIIB-NA1/NA1–FcγRIIIA-V/V158 and FcγRIIIB-NA2/NA2–FcγRIIIA-F/F158 frequencies were increased at the expense of FcγRIIIB-NA1/NA1–FcγRIIIA-F/F158 and FcγRIIIB-NA2/NA2–FcγRIIIA-V/V158 ($\chi^2 = 13{\cdot}5$, $P = 0{\cdot}008$).

Table 3. Estimated frequencies of FcγRIIA–FcγRIIIA–FCγRIIIB allele combinations (haplotypes) on chromosome 1

Haplotype	Sami population	Norwegian population
H/V/NA1	1%	4%
H/V/NA2	13%	14%
H/F/NA1	32%	10%
H/F/NA2	27%	12%
R/V/NA1	0%	2%
R/V/NA2	0%	11%
R/F/NA1	9%	15%
R/F/NA2	17%	32%

Haplotypes

Distributions of chromosomal allele combinations (haplotypes) were significantly different between the Norwegian ($n = 272$; 544 chromosomes) and the Sami ($n = 200$; 400 chromosomes) participants. The H/F/NA1, H/F/NA2 haplotypes were more frequent and the and R/V/NA2 and R/F/NA2 less frequent among the Samis ($P < 0{,}0001$, Table 3).

Discussion

FcγRIIA, FcγRIIIA and FcγRIIIB gene polymorphisms differ in these Sami and Norwegian populations. The Norwegians displayed an allele frequency and genotype similar to what has been found among other Caucasians.[16,18,28,29] FcγR polymorphisms in the Sami population have not been published previously. FcγR genotype and allele frequency distribution among the Sami participants resembled previous findings of populations from eastern Asia and the Indian subcontinent.[16,28] The Samis constitute about 25 000 of the inhabitants in Troms and Finnmark, the two northernmost counties of Norway.[21] The genetic distance between the Samis and other Europeans has been shown to be significantly greater than between any other pair of European populations.[20] Their genetic origin is unknown, but recent evidence, based on mitochondrial DNA and Y-chromosomes, suggests that their genetic separation is best explained by assuming that they are descendants of a narrow subset of Europeans.[30]

The FcγRIIA, FcγRIIIA and FcγRIIIB genes are most likely derived from a common gene and are clustered in very close proximity on chromosome 1q22 (within 1·1 kb).[27] One would therefore expect the genes to be non-randomly distributed, as this study demonstrated for both populations. These findings are supported by previous reports of non-random distribution in FcγR polymorphism,[27,31] although others have failed to show this linkage disequilibrium.[18] The limited number of subjects studied in most previous studies could probably explain these discrepancies. The linkage disequilibrium found in this study, however, differed between the Norwegian and the Sami populations. Thus, our results support the hypothesis by Van der Pol *et al.*[27] that FcγR alleles are preferably transmitted in specific combinations and that the FcγR genotype frequencies are also reflected in the distribution of chromosomal FcγR allele combinations. When grouped into haplotypes, the Sami displayed a clustering to four chromosomal combinations (89% of chromosomes). This did not occur in the Norwegian population, but resembles the findings of Van der Pol *et al.* in a Japanese population.[27] Linkage disequilibrium has also been demonstrated between Duffy group antigens and FcγRIIIB genotypes.[32] Several interesting genes encoding for immune-related molecules such as C-reactive protein, IgE receptor I, selectins E and L, lymphocyte antigen 9, the interleukin-6 receptor, Duffy blood group antigens and the pentaxin family proteins are located in close proximity to the FcγR genes.[27] Thus, linkage disequilibrium may exist between other adjacent genes and FcγR genotypes. This may complicate the association between FcγR polymorphism and disease and should be evaluated in future studies.

Differences in FcγR polymorphisms probably reflect varying evolutionary challenges[16] and could greatly influence the responses to and prevalence of infectious and autoimmune diseases in the Sami and Norwegian populations. Epidemiological studies in Norway have demonstrated that the prevalence of MS is much lower in the Sami population than in the Norwegian population.[21,33] This has led to the suggestion that the Samis are resistant to the disease because of their genetic origin.[34] We have previously found that Norwegians with the FcγRIIIB-NA1/NA1 and, to a lesser extent, FcγRIIA-H/H genotypes had a more benign course of MS. Co-ligation of FcγRIIA and FcγRIIIB results in a synergistic phagocytic response,[35] resulting in improved clearance of circulating immune complexes. Thus our findings suggest that homozygosity for FcγRIIIB-NA1/NA1 and FcγRIIA-H/H with a more efficient clearance of circulating antibodies improve clinical outcome.[29] Although our findings have not been confirmed in a Dutch population,[36] it is interesting that the NA1/NA1 and H/H genotypes were enriched among the Samis. Similarly, the Japanese population, also displaying a high prevalence of the NA1/NA1 and H/H genotypes[27] has a low prevalence of MS.[34]

The prevalence of ankylosing spondylitis is higher among the Samis than the Norwegians.[23] This may be a result of the higher prevalence of HLA-B27 among the Samis.[37] The relevance of FcγR polymorphism in ankylosing spondylitis is unknown, however. Low frequencies of allergic rhinoconjunctivitis and atopic dermatitis have been reported among the Samis.[22] Although certain FcγR-polymorphisms can be risk factors for autoimmunity,[3] polymorphisms have not been demonstrated to be important in the development of atopic disease.[38] FcγR polymorphisms have been linked to several other

immune-mediated diseases such as systemic lupus erythematosus,[3] antiphospholipid syndrome[3] and rheumatoid arthritis.[39,40] There have, however, not been any epidemiological studies of these diseases in the Sami population.

FcγRIIA-R131 and FcγRIIIB-NA2 are associated with increased risk of chronic infections[28] and influence the prognosis of various infectious diseases. This is especially well documented for encapsulated bacteria. FcγRIIA-R-131 negatively influences the prognosis of both streptococcal and meningococcal disease.[5,6] FcγRIIA-H-131 represents the only leucocyte receptor capable of interacting with IgG2, and the fact that IgG2 deficiency predisposes to pneumococcal disease emphasizes the importance of IgG2 in the defense against encapsulated bacteria.[41] The Sami population displayed a significantly higher frequency of the FcγRIIA-H/H and FcγRIIIB-NA1/NA1 genotypes. However, they had a higher frequency of the FcγRIIIA-F/F genotype. Because FcγRIIIA is expressed on macrophages and natural killer cells, this could indicate lower natural killer cell activity in the Sami population. Whether the various FcγR polymorphisms found among the Samis are associated with a different pattern of infections from Norwegians remains to be studied.

Acknowledgements

We thank all the individuals who have contributed with blood samples to this study. This work was supported by grants from the Bergen MS Society, the Norwegian Research Council (project number 15488/V40), the Odd Fellow, the Norwegian Society of Multiple Sclerosis and Kjell Alme's Legacy for Research in Multiple Sclerosis, Bergen. We thank Kibret Mazengia for technical assistance, Sonja Gavasso for valuable comments and Jan Aarseth for assistance with the statistical calculations. We also thank Siri Flåm, Institute of Immunology, University of Oslo, Rikshospitalet and Rikshospitalet University Hospital for technical assistance.

References

1 Kimberly RP, Salmon JE, Edberg JC. Receptors for immunoglobulin G. Molecular diversity and implications for disease. *Arthritis Rheum* 1995; **38**:306–14.

2 Salmom JE, Pricop L. Human receptors for immunoglobulin G. key elements in the pathogenesis of rheumatic disease. *Arthritis Rheum* 2001; **44**:739–50.

3 Vedeler CA, Myhr KM, Nyland H. Fc receptors for immunoglobulin G – a role in the pathogenesis of Guillain–Barré syndrome and multiple sclerosis. *J Neuroimmunol* 2001; **118**:187–93.

4 Karassa FB, Trikalinos TA, Ioannidis JPA. The role of FcγRIIA and IIIA polymorphism in autoimmune disease. *Biomed Pharmacother* 2004; **58**:286–91.

5 Yuan FF, Wong M, Pererva N, Keating J, Davis AR, Bryant JA, Sullivan JS. FcγRIIa polymorphisms in *Streptococcus pneumoniae* infection. *Immunol Cell Biol* 2003; **81**:192–5.

6 Domingo P, Muñiz-Diaz E, Baraldès MA *et al.* Relevance of genetically determined host factors to the prognosis of meningococcal disease. *Eur J Clin Microbiol Infect Dis* 2004; **23**:634–7.

7 Omi K, Ohashi J, Patarapotikul J, Hananantachai H, Naka I, Looareesuwan S, Tokunaga K. Fcγ receptor IIA and IIIB polymorphisms are associated with susceptibility to cerebral malaria. *Parasitol Int* 2002; **51**:361–6.

8 Rekand T, Langeland N, Aarli JA, Vedeler CA. Fcγ receptor IIIA polymorphism as a risk factor for acute poliomyelitis. *J Infect Dis* 2002; **186**:1840–3.

9 Louis E, El Ghoul Z, Vermeire S *et al.* Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther* 2004; **19**:511–9.

10 Gruel Y, Pouplard C, Lasne D, Magdelaine-Beuzelin C, Charroing C, Watier H. The homozygous FcγRIIIa-158V genotype is a risk factor for heparin-induced thrombocytopenia in patients with antibodies to heparin/platelet factor 4 complexes. *Blood* 2004; **104**:2791–3.

11 Yuan FF, Watson N, Sullivan JS, Biffin S, Moses J, Geczy AF, Chapman JR. Association of Fc gamma receptor IIa polymorphisms with acute renal-allograft rejection. *Transplantation* 2004; **78**:766–9.

12 Warmerdam PAM, van de Winkel JGJ, Gosselin EJ, Capel PJA. Molecular basis for a polymorphism of human Fcγ receptor II (CD32). *J Exp Med* 1990; **172**:19–25.

13 Bredius RG, Fijen CA, De Haas M, Kuijper EJ, Weening RS, Van de Winkel JG, Out TA. Role of neutrophil Fc gamma RIIa (CD32) and Fc gamma RIIIb (CD16) polymorphic forms in phagocytosis of human IgG1- and IgG3-opsonized bacteria and erythrocytes. *Immunology* 1994; **83**:624–30.

14 Wu J, Edberg JC, Redecha PB, Bansal V, Guyre PM, Coleman K, Salmon JE, Kimberly RP. A novel polymorphism of FcγRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. *J Clin Invest* 1997; **100**:1059–70.

15 Koene HR, Kleijer M, Algra J, von Roos D, dem Borne AEGK, de Haas M. FcγRIIIa-158V/F polymorphism influences the binding of IgG by natural killer cell FcγRIIIa, independently of the FcγRIIIa-48L/R/H phenotype. *Blood* 1997; **90**:1109–14.

16 Lehrnbecher T, Foster CB, Zhu S, Leitman SF, Goldin LR, Huppi K, Chanock SJ. Variant genotypes of the low-affinity Fcγ receptors in two control populations and a review of low-affinity Fcγ receptor polymorphisms in control and disease populations. *Blood* 1999; **94**:4220–32.

17 Schie RCAA, Wilson ME. Evaluation of human FcγRIIA (CD32) and FcγIIIB (CD16) polymorphisms in Caucasians and African-Americans using salivary DNA. *Clin Diagn Lab Immunol* 2000; **7**:676–81.

18 Van Den Berg L, Myhr KM, Kluge B, Vedeler CA. Fcγ receptor polymorphisms in populations in Ethiopia and Norway. *Immunology* 2001; **104**:87–91.

19 Carrington CVF, Norman PJ, Vaughan RW, Kondeatis E, Ramdath DD, Hameed K, Stephens HA. Analysis of Fc gamma receptor II (CD32) polymorphisms in populations of African and South Asian ancestry reveals east–west geographic gradients of allele frequencies. *Eur J Immunogenet* 2003; **30**:375–9.

20 Cavalli-Sforza LL, Menozzi P, Piazza A. *The History and Geography of Human Genes*. Princeton: Princeton University Press, 1994.

21 Grønlie SA, Myrvoll E, Hansen G, Grønning M, Mellgren SI. Multiple sclerosis in north Norway, and first appearance in an indigenous population. *J Neurol* 2000; **247**:129–33.

22 Falk ES. Atopic disease in Norwegian Lapps. *Acta Derm Venereol Suppl* 1993; **182**:10–4.

23 Johnsen K, Gran JT, Dale K, Husby G. The prevalence of ankylosing spondylitis among Norwegian Samis (Lapps). *J Rheumatol* 1992; **19**:1591–4.

24 Botto M, Theodoridis E, Thompson EM *et al.* Fc gamma RIIa polymorphism in systemic lupus erythematosus (SLE): no association with disease. *Clin Exp Immunol* 1996; **104**:264–8.

25 Leppers-van de Straat FGJ, van der Pol WL, Jansen MD *et al.* A novel PCR-based method for direct Fcγ receptor IIIa (CD16) allotyping. *J Immunol Meth* 2000; **242**:127–32.

26 Bux J, Stein EL, Santoso S, Mueller-Eckhardt C. NA gene frequencies in the German population, determined by polymerase chain reaction with sequence-specific priemrs. *Transfusion* 1995; **35**:54–7.

27 Van der Pol WL, Jansen MD, Sluiter WJ *et al.* Evidence for non-random distribution of Fcγ receptor genotype combinations. *Immunogenetics* 2003; **55**:240–6.

28 Van der Pol W, Van de Winkel JGJ. IgG receptor polymorphisms: risk factors for disease. *Immunogenetics* 1998; **48**:222–32.

29 Myhr KM, Raknes G, Nyland H, Vedeler C. Immunoglobulin G Fc-receptor (FcγR) IIA and IIIB polymorphisms related to disability in MS. *Neurology* 1999; **52**:1771–6.

30 Tambets K, Rootsi S, Kivisild T *et al.* The western and eastern roots of the Sami – the story of genetic 'outliers' told by mitochondrial DNA and Y chromosomes. *Am J Hum Genet* 2004; **74**:661–82.

31 Edberg JC, Langefeld CD, Wu J *et al.* Genetic linkage and association of Fcγ receptor IIIA (CD16A) on chromosome 1q23 with human systemic lupus erythematosus. *Arthritis Rheum* 2002; **46**:2132–40.

32 Schnackenberg L, Flesch BK, Neppert J. Linkage disequilibria between Duffy blood groups, Fc gamma IIa and Fc gamma IIIb allotypes. *Exp Clin Immunogenet* 1997; **14**:235–42.

33 Grønning M, Mellgren SI. Multiple sclerosis in the two northernmost counties of Norway. *Acta Neurol Scand* 1985; **72**: 321–7.

34 Rosati G. The prevalence of multiple sclerosis in the world: an update. *Neurol Sci* 2001; **22**:117–39.

35 Edberg JC, Kimberly RP. Modulation of Fcγ and complement receptor function by the glycosyl-phosphatidylinositol anchored form of FcγRIII. *J Immunol* 1994; **152**:5826–35.

36 Breij ECW, van der Pol WL, van Winsen L, Jansen MD, Dijkstra CD, van de Winkel JG, Uitdehaag BM. No association of FcγRIIa, FcγRIIIa and FcγRIIIb polymorphisms with MS. *J Neuroimmunol* 2003; **140**:210–5.

37 Thorsby E, Bartlie A, Teisberg P. HL-A polymorphism of Norwegian Lapps. *Tissue Antigens* 1971; **1**:137–46.

38 Pawlik A, Carlson L, Meisel P, Czaja-Bulsa G, Mokrzycka M, Gawronska-Szklarz B. The FcγRIIa polymorphism in children with atopic disease. *Int Arch Allergy Immunol* 2004; **133**:233–8.

39 Brun JG, Madland TM, Vedeler CA. Immunoglobulin G Fc receptor (FcγR) IIA IIIA and IIIB polymorphisms related to the severity in rheumatoid arthritis. *J Rheumatol* 2002; **29**: 1135–40.

40 Morgan AW, Keyte VH, Babbage SJ *et al.* FcγRIIIA-158V and rheumatoid arthritis: a confirmation study. *Rheumatology (Oxford)* 2003; **42**:528–33.

41 Jefferis R, Kumararatne DS. Selective IgG subclass deficiency: quantification and clinical relevance. *Clin Exp Immunol* 1990; **81**:357–67.