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**FcγRIIIa-158V/F Polymorphism Influences the Binding of IgG by Natural Killer Cell FcγRIIIa, Independently of the FcγRIIIa-48L/R/H Phenotype**

By Harry R. Koene, Marion Kleijer, Johan Algra, Dirk Roos, Albert E.G.Kr. von dem Borne, and Masja de Haas

We analyzed a genetic polymorphism of Fcγ receptor IIIa (CD16) that is present on position 158 (Phe or Val) in the membrane-proximal, IgG-binding domain. With a polymerase chain reaction–based allele-specific restriction analysis assay we genotyped 87 donors and found gene frequencies of 0.57 and 0.43 for FcγRIIIA-158F and -158V, respectively. A clear linkage was observed between the FcγRIIIA-158F and -48L genotypes on the one hand and the FcγRIIIA-158V and -48H or -48R genotypes on the other hand (χ² test: P < .001). To determine the functional consequences of this FcγRIIIA-158V/F polymorphism, we performed IgG binding experiments with natural killer (NK) cells from genotyped donors. All donors were also typed for the recently described triallelic FcγRIIIA-48L/R/H polymorphism. NK cells were treated with lactic acid to remove cell-associated IgG. FcγRIIIA⁴⁶.

**S**everal IgG Fc receptor (FcγR) polymorphisms that influence the binding of IgG have been described. On neutrophils, the FcγRIIIb-NA1 and -NA2 isoforms, which differ by four amino acids in the membrane-distal Ig-like loop of the receptor, interact differently with IgG-opsonized particles, and influence the interaction of the receptor with FcγRIIA. On FcγRIIa, the extensively investigated high responder (HR) polymorphism on amino-acid position 131 in the membrane-proximal, IgG-binding domain is critical for the interaction with human IgG₂. Moreover, the FcγRIIIa-131R/H polymorphism was found to be associated with several diseases, such as bacterial infections in children, heparin-induced thrombocytopenia, juvenile periodontitis, and systemic lupus erythematosus.⁴

Previously, Ravetch and Perussia described a polymorphism in the membrane-proximal domain of FcγRIIIa. A nucleotide substitution at position 559 of FcγRIIIA predicts either a valine or a phenylalanine at amino-acid position 158 of FcγRIIIa. Because the IgG binding site is most probably located in this part of FcγRIIIa, we determined the gene frequency and functional consequences of this polymorphism in the context of the recently described FcγRIIIA-48L/R/H polymorphism. As expected, a clear although incomplete linkage was observed between the two polymorphisms. Moreover, we found that the previously described differences in binding between the FcγRIIIA-158F and -48L/R/H isoforms of IgG and of some of the CD16 monoclonal antibodies (MoAbs) are attributable to the FcγRIIIA-158V phenotype.

**MATERIALS AND METHODS**

MoAbs. Anti-pan FcγIII (CD16) MoAbs used were CLB-FcγRIIap (mlgG2a) and MEM154 (mlgG1). B73.1 (mlgG1) reacts with NA1-FcγRIIIb and with FcγRIIIa, and was kindly provided by Dr B. Perussia (Thomas Jefferson University, Philadelphia, PA). MEM154 was obtained through the 5th Leukocyte Typing Workshop. Phycoerythrin (PE)-labeled Leu19 (CD56, mlgG1) was purchased from Becton Dickinson (San Jose, CA). Fluorescein isothiocyanate (FITC)-conjugated goat–antimouse Ig and irrelevant control MoAbs of the IgG1 and IgG2a subclasses were from the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB), Amsterdam, The Netherlands.

Isolation of cells. Fresh, EDTA-anticoagulated blood from healthy volunteers was diluted with two volumes of phosphate-buffered saline (PBS) and was centrifuged over a Ficoll gradient (Pharmacia Fine Chemicals AB, Upsala, Sweden) with a specific gravity of 1.076 g/mL. Peripheral blood mononuclear cells (PBMC) were obtained from the interphase and were washed twice with PBS, containing 0.2% (wt/vol) bovine serum albumin (BSA).

Flow cytometry. PBMC were incubated with CD16 MoAbs for 25 minutes at room temperature. The cells were washed with PBS/BSA, and were incubated with FITC-labeled goat–antimouse-Ig for 25 minutes at room temperature. Free F(ab')₂ regions of the conjugate were blocked with a mixture of irrelevant mlgG1 and mlgG2a. Thereafter, the cells were incubated with PE-labeled CD56. Only CD56⁺ lymphocytes were analyzed in a FACScan flowcytometer (Becton Dickinson).

FcγRIIIA-48L/R/H genotyping. Genotyping for the FcγRIIIA-48L/R/H polymorphism was performed as previously described, with a polymerase chain reaction (PCR)-based allele-specific restriction analysis assay. Briefly, a 91-bp FcγRIIIA-specific fragment containing the polymorphic site was amplified from genomic DNA and digested with Mnl I. Digested fragments were electrophoresed in 10% acryl amide gels, stained with ethidium bromide, and visualized with UV light. Homozygous FcγRIIIA-48L individuals showed 40-bp, 34-bp, and 17-bp bands, whereas PCR fragments of individuals carrying no or only one FcγRIIIA-48L allele showed a 51-bp band. The genotype of these latter individuals was determined by direct sequencing of the amplified fragments, using one of the PCR primers, end-labeled with ³²P (Amersham International, Buckinghamshire, UK), with the Life Technologies cycle sequencing kit, following...

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ing the instructions of the manufacturer (Life Technologies, Gaithersburg, MD).

**FcγRIIIA-158VF genotyping.** Genotyping of the FcγRIIIA-158VF polymorphism was performed by means of a (nested) PCR-based allele-specific restriction analysis assay. Two FcγRIIIA gene-specific primers (sense A013: 5'-ATA TTT ACA GAA TGG CAC AGG-3'; antisense A012: 5'-GAC TTG GTA CCC AGG TTG AA-3'; italic characters denote mismatches that were introduced to increase specificity) were used to amplify a 1.2-kb fragment containing the polymorphic site. This PCR assay was performed with 5 ng of genomic DNA, 150 ng of each primer, 200 μmol/L of each dNTP, and 2 U of Taq DNA polymerase (Promega, Madison, WI), diluted in a buffer recommended by the manufacturer in a total volume of 50 μL in a Perkin Elmer Cetus laser cycler (Norwalk, CT). The first PCR cycle consisted of 10 minutes denaturation at 95°C, 1½ minute primer annealing at 56°C, and 1½ minute extension at 72°C. This was followed by 35 cycles in which the denaturing time was decreased to 1 minute. The last cycle was followed by 8 minutes at 72°C to complete extension. The sense primer in the second PCR contained a NlaIII restriction site only in FcγRIIIA-158VF-encoding DNA (A014: 5'-aTc tga tga gCT TGA GTG ATG ATG TTC AC-3'). This “nested” PCR was performed with 1 μL of the amplified fragment, 150 ng of each primer, 200 μmol/L of each dNTP, and 2 U of Taq DNA polymerase, diluted in the recommended buffer. The first cycle consisted of 5 minutes' denaturing at 95°C, 1 minute primer annealing at 64°C, and 1 minute extension at 72°C. This was followed by 35 cycles in which the denaturing time was 1 minute. The last cycle was followed by 9½ minutes at 72°C to complete extension. The 94-bp fragment was digested with NlaIII, and digested fragments were electrophoresed in 10% polyacrylamide gels, stained with ethidium bromide, and visualized with UV light. Cycle sequencing of first-round fragments to check for specificity was performed with three end-labeled primer A016 with the Life Technologies cycle sequencing kit. Genomic DNA of individuals whose FcγRIIIA encoding cDNA sequence was known were used to optimize the PCR assay.

**IgG-binding experiments.** Quantification of IgG binding to natural killer (NK) cells of genotyped donors was performed as previously described.17 In short, mononuclear cells were pretreated with 0.1% (wt/vol) lactic acid (pH 3.9) to remove NK-cell-associated IgG. This treatment did not alter FcγRIIIA expression as measured with CD16 MoAb CLBFcRgran1 (not shown). The cells were incubated with saturating amounts of human IgG subclasses purified from sera of patients suffering from multiple myeloma. The antibodies were at least partially aggregated, because binding to PMN was observed with the IgG1 and IgG3 preparations (not shown). After washing, bound IgG was detected by FITC-labeled F(ab')2 fragments of goat–anti-human-IgG (Kallestad, South Austin, TX), and NK cells were identified with PE-labeled CD56. Only CD56+ lymphocytes were analyzed in a FACSscan flow cytometer.

**Statistical analysis.** The data were analyzed with the Student’s t-test and the χ2-test. Data with different standard deviations (SDs) were compared with the Welch’s approximate t-test. P values below .05 were considered significant.

**RESULTS**

**FcγRIIIA-158VF genotyping.** An FcγRIIIA-derived fragment containing the polymorphic site was amplified from genomic DNA with two FcγRIIIA gene-specific primers. Subsequently, a nested PCR was performed in which an NlaIII restriction site was created only in the FcγRIIIA-158VF allele. Figure 1 shows digestion of the 94-bp PCR fragment with NlaIII. In lanes 1 to 3, PCR fragments from homozygous FcγRIIIA-158FF donors are not digested by NlaIII. In lanes 4 to 6, three bands of 94 bp, 61 bp, and 33 bp are visible, indicating the FcγRIIIA-158VF heterozygosity of these individuals. Although the fragments in lanes 7 to 9 were from homozygous FcγRIIIA-158VV donors, a 94-bp band of low intensity remained, which was not removed by longer digestion, higher enzyme concentrations, or use of isoosmichromogen Np. The 94-bp band in these donors was not a result of amplification of FcγRIIIB fragments due to unspecificity of the first-round PCR, because the FcγRIIIA gene carries a G at nucleotide position 559, which results in digestion by NlaIII. Direct sequencing of several first-round PCR products confirmed the FcγRIIIA gene specificity of the assay and the FcγRIIIA-158 genotype of the donors. Genotyping of 87 healthy white individuals yielded gene frequencies of 0.57 and 0.43 for FcγRIIIA-158F and −158V, respectively.

Table 1 displays the correlation between the FcγRIIIA-48 and the FcγRIIIA-158 phenotypes. A clear linkage was observed between the FcγRIIIA-158VF and the FcγRIIIA-48L/R homozygosities (χ2-test, P < .001). All FcγRIIIA-158VF individuals were homozygous FcγRIIIA-48LL, whereas all donors with heterozygous FcγRIIIA-48LR or −48LH genotypes carried at least one FcγRIIIA-158 allele.

**Binding of CD16 MoAbs to NK cells of genotyped donors.** To determine the influence of the FcγRIIIA-158VF and -48L/R/R homozygosities on the binding of a panel of CD16 MoAbs, we investigated binding patterns by NK cells of genotyped donors (Table 2). The binding of MoAb CLBFcRgran1 was not significantly different among NK cells of genotyped donors. In contrast, FcγRIIIA-158VF-positive NK cells from donors homozygous positive for FcγRIIIA-48L bound more MEM154 than did NK cells of FcγRIIIA-158FF-positive donors (Welch’s approximate t-test, P = .01). In turn, FcγRIIIA-158VF NK cells from donors who had only one FcγRIIIA-48L allele bound less MEM154 than did FcγRIIIA-158VV NK cells (P = .04).

Comparison of NK cells of FcγRIIIA-158VF phenotyped donors who were either homozygous FcγRIIIA-48LL, or heterozygous −48LR or −48LH showed different binding patterns with MoAb B73.1. NK cells positive for the FcγRIIIA-48R or −48H isoforms showed reduced binding of B73.1 compared with FcγRIIIA-48LL homozygous NK cells (P = .05). Binding of MoAb MEM154 was equal among these donors. Three FcγRIIIA-158VV individuals who were either homozygous FcγRIIIA-48RR or −48HH were tested. Binding of MEM154 to cells of these donors was equal compared to the binding to NK cells from FcγRIIIA-158VV individuals with a heterozygous FcγRIIIA-48 phenotype, whereas the binding of B73.1 was diminished (Table 2).

**Binding of IgG subclasses by FcγRIIIAnε-158 isozymes in the context of the FcγRIIIAnε-48 phenotype.** To determine the functional consequences of the FcγRIIIA-158VF polymorphism, we compared the IgG binding capacity of NK cells from genotyped donors. We studied the differences in IgG binding between individuals who had different
**Fig 1.** NlaIII restriction analysis of the 94-bp FcγRIIIA-specific fragment, containing the polymorphic nucleotide 559. A 1.2-kb FcγRIIIA-specific fragment was amplified from genomic DNA, followed by a nested PCR. The sense primer of this nested PCR contained a mismatch that introduced a NlaIII restriction site only in the FcγRIIIA-158V (559G) allele. Homozygous FcγRIIIA-158FF fragments were not digested (lanes 1 through 3). Three bands (94 bp, 61 bp, and 33 bp) were visible in heterozygous individuals, whereas homozygous FcγRIIIA-158VV fragments were maximally digested (lanes 7 through 9). A 92-bp fragment of low intensity remained in homozygous 559G fragments (lanes 7 through 9).

**FcγRIIIA-158V/F genotypes,** but were identical regarding the FcγRIIIA-48L/R/H genotype. Preincubation of PBMC with F(ab’) fragments of CD16 MoAb CLBFcRgran1 reduced the binding of IgG to less than 10% of control values, indicating that the interaction was FcγRIIIa-mediated (data not shown). As shown in Table 3, lactic acid-treated homozygous FcγRIIIa-48LL NK cells from individuals heterozygous at position 158 of FcγRIIIa bound more IgG3 than did NK cells from FcγRIIIa-158FF phenotyped donors (P = .02). Although a trend was observed, the difference in binding of IgG1 was not statistically significant. In one single experiment, NK cells from the one available donor who was homozygous FcγRIIIa-48LL as well as -158VV bound more IgG3 than did FcγRIIIa-158FF or heterozygous donors, without clear differences in binding of IgG1 (data not shown). In individuals who were heterozygous for the FcγRIIIa-48L/R/H polymorphism, FcγRIIIa-158VV-positive NK cells bound more IgG1 compared with FcγRIIIa-158VF-positive NK cells (Table 3; Welch’s approximate t-test, P = .03). For these donors, the differences in binding of IgG3 were not statistically significant, although a trend was observed. When we determined the levels of NK-cell–associated IgG of freshly isolated NK cells, we observed that FcγRIIIa-158FF-positive cells carried less IgG than did FcγRIIIa-158VV-positive cells. Comparing NK cells from donors of the same FcγRIIIa-48L/R/H phenotype, we observed a trend toward higher levels of cytolytic IgG bound by FcγRIIIa-158VF and -158VV-positive cells, as compared with FcγRIIIa-158FF-positive cells (Table 3). The levels of NK-cell–associated IgG of FcγRIIIa-48LL and -158VF-positive NK cells did not significantly differ from that of FcγRIIIa-48LR or -48LH NK cells of the same -158VF phenotype.

To exclude any effect of the triallelic FcγRIIIa-48L/R/H polymorphism on IgG binding, we compared FcγRIIIa-48LL-positive NK cells with FcγRIIIa-48LR or -48LH-positive NK cells from donors who were all heterozygous FcγRIIIa-158VF. As shown in Table 3, no statistically significant differences were observed in either the amount of NK-cell–associated IgG or in the binding of IgG subclasses to lactic acid–treated NK cells. Therefore, we depicted the results of IgG-binding experiments, comparing FcγRIIIa-158FF NK-

### Table 1. FcγRIIIA-158V/F Genotypes in White Individuals (n = 87), Typed for FcγRIIIA-48L/R/H

<table>
<thead>
<tr>
<th>Genotype</th>
<th>FcγRIIIA-158</th>
<th>Total</th>
<th>FcγRIIIA-48L/R/H Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>48LL</td>
<td>48LR</td>
</tr>
<tr>
<td>559T/T</td>
<td>158FF</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>559G/T</td>
<td>158VF</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>559G/G</td>
<td>158VV</td>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>

Gene frequencies are 0.57 and 0.43 for FcγRIIIa-158F and FcγRIIIa-158V, respectively. A clear linkage was observed between the FcγRIIIA-158F and the FcγRIIIa-48L alleles, as well as between the FcγRIIIa-158V and either the FcγRIIIa-48R or -48H alleles (χ² test; P < .001 in both cases).

* A dash (—) denotes that in this study none of the tested donors had this genotype.
† In a previous study we described one healthy individual and two unrelated patients suffering from recurrent bacterial and viral infections who were homozygous FcγRIIIa-48H/H (De Vries, unpublished data, 1996 and ref 18). These three donors were found to be homozygous FcγRIIIa-158VV.
cells with FcγRIIIa-158VV NK cells, disregarding the FcγRIIIa-48 phenotype (Fig 2). Significant differences in levels of IgG1 (P = 0.007), IgG3 (0.005), IgG4 (.02), and cytophilic IgG (.004) were observed.

**DISCUSSION**

Recently we identified a triallelic polymorphism in the membrane-distal Ig-like domain of FcγRIIIa, in which a leucine, an arginine, or a histidine can be present at amino acid position 48. In the present report, we functionally characterized a previously described genetic polymorphism of FcγRIIIa, encoding either a phenylalanine (F) or a valine (V) at amino acid position 158 in the membrane-proximal Ig-like loop of FcγRIIIa. We determined that the gene frequencies for FcγRIIIa-158F and FcγRIIIa-158V were 0.57 and 0.43, respectively. The FcγRIIIa-158FF genotype was shown to be clearly linked to the FcγRIIIa-48L/R/H genotypes, whereas the FcγRIIIa-158VV genotype was found to be linked to FcγRIIIA-48R. A linkage between allotypes of the FcγRIIIa-158FF and the FcγRIIIa-48L/R/H polymorphisms was expected because the two polymorphisms are located within the same gene.

In our previous work, we attributed differences in binding of several CD16 MoAbs to the amino acid present on position 48 of FcγRIIIa. We now show that the binding of MEM154 depends on the presence of a valine at amino acid position 158 of FcγRIIIa and is not influenced by the amino acid polymorphism at position 48. These findings are in conformity with data from Tamm and Schmidt, who found that the epitope recognized by MEM154 is located in the membrane-proximal domain. We did not observe any effect of the FcγRIIIa-158V/F polymorphism on B73.1 binding but confirmed our previous observations that only the amino acid at position 48 influenced the binding of MoAb B73.1.

The membrane-proximal domain, carrying the FcγRIIIa-158VF polymorphism, is generally accepted to contain the IgG-binding site in FcγRs, and experiments with mutants of FcγRIIIb showed that the membrane-proximal loop is essential for IgG binding in FcγRIIib. To study the functional consequences of the FcγRIIIa-158VF polymorphism in the context of the FcγRIIIa-48L/R/H polymorphism, we performed IgG binding experiments with NK cells from genotyped donors. NK cells from homozygous FcγRIIIa-158VF-positive individuals bound more IgG1 and IgG3 than did FcγRIIIa-158FF-positive NK cells, irrespective of the amino acid present on position 48 of the receptor. NK cells of FcγRIIIa-158VF heterozygous donors showed intermediate levels of IgG binding, indicating a gene-dosage effect. These data indicate that the donor-dependent differences in IgG binding of FcγRIIIa isosforms are attributable to the

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**Table 2. CD16 MoAb Binding (mean fluorescence intensities ± SD) of NK Cells From Individuals Genotyped for FcγRIIIA Polymorphisms**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>MoAb</th>
<th>Control mlgG2a</th>
<th>CLBFcRgran1</th>
<th>MEM154</th>
<th>B73.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>48LL</td>
<td>158FF</td>
<td>12 ± 6</td>
<td>1,539 ± 257</td>
<td>42 ± 20</td>
<td>303 ± 176</td>
</tr>
<tr>
<td>48LL</td>
<td>158VF</td>
<td>8 ± 4</td>
<td>1,713 ± 719</td>
<td>460 ± 218*</td>
<td>248 ± 105</td>
</tr>
<tr>
<td>48LR or 48LH</td>
<td>158VF</td>
<td>6 ± 2</td>
<td>1,443 ± 504</td>
<td>323 ± 182</td>
<td>121 ± 511</td>
</tr>
<tr>
<td>48LR or 48LH</td>
<td>158VV</td>
<td>10 ± 5</td>
<td>1,102 ± 298</td>
<td>718 ± 341†</td>
<td>151 ± 117</td>
</tr>
<tr>
<td>48HH§</td>
<td>158VV</td>
<td>7</td>
<td>1,694</td>
<td>892</td>
<td>55</td>
</tr>
<tr>
<td>48RR†</td>
<td>158VV</td>
<td>15</td>
<td>1,443</td>
<td>642</td>
<td>103</td>
</tr>
</tbody>
</table>

At least three donors of each genotype were tested. Data were analyzed with the Student’s t-test the and Welch’s approximate t-test. * P-values below .05 were considered significant.

† Significantly different from FcγRIIIa-158F/F individuals of the same FcγRIIIA-48 genotype.

§ Two individuals were tested; one healthy control and one patient suffering from recurrent viral infections.

**Table 3. Binding of Human IgG Subclasses of NK Cells From Individuals Genotyped for FcγRIIIA Polymorphisms (MFI ± SD)**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Subclass</th>
<th>IgG1 ± SD</th>
<th>IgG2 ± SD</th>
<th>IgG3 ± SD</th>
<th>IgG4 ± SD</th>
<th>Cytophilic IgG ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>48LL</td>
<td>158FF</td>
<td>913 ± 317</td>
<td>58 ± 33</td>
<td>390 ± 131</td>
<td>106 ± 104</td>
<td>337 ± 159</td>
</tr>
<tr>
<td>48LL</td>
<td>158VF</td>
<td>1,257 ± 608</td>
<td>124 ± 126</td>
<td>912 ± 286*</td>
<td>413 ± 178</td>
<td>695 ± 405</td>
</tr>
<tr>
<td>48LR or 48LH</td>
<td>158VF</td>
<td>1,243 ± 194</td>
<td>155 ± 133</td>
<td>746 ± 230</td>
<td>548 ± 202</td>
<td>1,139 ± 542</td>
</tr>
<tr>
<td>48LR or 48LH</td>
<td>158VV</td>
<td>1,814 ± 507†</td>
<td>173 ± 98</td>
<td>1,053 ± 487</td>
<td>487 ± 286</td>
<td>1,788 ± 796</td>
</tr>
</tbody>
</table>

At least three donors of each genotype were tested. Data were analyzed with the Student’s t-test and the Welch’s approximate t-test. * P-values below .05 were considered significant.

† Significantly different from FcγRIIIa-158F/F cells of the same FcγRIIIA-48 genotype.
**ACKNOWLEDGMENT**

We thank Dr E. De Vries (Department of Pediatrics of the University Hospital Leiden, Leiden, The Netherlands) for providing the patient samples.

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