CONCISE REPORT

The F158V polymorphism in FcγRIIIA shows disparate associations with rheumatoid arthritis in two genetically distinct populations

A Milicic, R Misra, S Agrawal, A Aggarwal, M A Brown, B P Wordsworth

**Objectives:** To investigate the association of the FcγRIIIA gene with rheumatoid arthritis (RA) in two genetically distinct groups: a white group from the United Kingdom and a northern Indian group.

**Methods:** The distributions of the two alleles of the FcγRIIIA F158V polymorphism were determined in 398 white patients from the United Kingdom and 63 Indian patients with RA and compared with those from 289 United Kingdom and 93 Indian healthy controls, respectively.

**Results:** Among the Indian patients, the frequency of the rare 158V allele and the proportion of 158V homozygotes were reduced (relative risk (RR)=0.3, 95% confidence interval (CI) 0.1 to 1.1, p<0.06), reaching statistical significance for carrying the 158V phenotype relative to 158FV or FF (RR=0.2, 95% CI 0.05–0.9, p<0.02). Conversely, no significant deviation in allelic frequencies was noted between the patients and controls from the United Kingdom.

**Conclusions:** The F158V phenotype showed a weak protective effect against developing RA in the Indian group. However, this sample was small (resulting in a low power for statistical analysis) and no independent confirmation was found in the larger white United Kingdom group. Thus the FcγRIIIA locus is unlikely to be of major importance in causing RA.

Rheumatoid arthritis (RA) is thought to have an important genetic component, with heritability estimated at around 60%. An oligogenic contribution is suspected, but to date only the HLA-DRB1 locus, contributing up to 40% of the genetic component of the disease, has been identified with certainty.

Rheumatoid arthritis is characterised by inflammation in the synovial joints and the presence of rheumatoid factor (RF)—autoantibodies directed against the (Fc) region of IgG—in the peripheral blood and the synovial fluid. IgG rheumatoid factors in particular have been associated with severe disease. These autoantibodies can self associate into immune complexes which, through the interaction with their receptors, trigger inflammatory events and have been implicated in the pathogenesis of RA.

The receptors for IgG recognise the Fc region of the immunoglobulin and divide into three main classes: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16), all of which are encoded at loci on chromosome 1q21–24. CD16 has two forms, IIIA and IIIB, encoded by the highly homologous FcγRIIA and FcγRIIB genes. The Fcγ receptor IIIA (FcγRIIA) is a transmembrane molecule of moderate affinity, involved in signal transduction on binding to the Fc region of IgG. It is expressed on the surface of natural killer (NK) cells, macrophages, differentiating monocytes, and γδ T cells and is the key mediator in some immune defence functions including degranulation, phagocytosis, antibody dependent cytotoxicity (ADCC), transcription of cytokine genes, and release of inflammatory mediators. Studies of FcγRIIA deficient mice have shown an important role for this receptor in inflammatory responses and immune complex mediated disease.

A single nucleotide polymorphism exists at position 559 (T/G) of the FcγRIIIA molecule, which results in a phenylalanine (F) to valine (V) substitution at residue 158 (or 176 in some publications). It has been reported that IgG stimulation of NK cells from FcγRIIIA-158Val homozygous people (158VV) results in higher Ca2+ influx, higher concentrations of interleukin-2 (IL2) receptor (CD25) expression, and reduced survival of NK cells after activation induced cell death when compared with 158FV heterozygotes or 158FF homozygotes. IgG binding studies have also shown that NK cells from 158VV homozygotes have a higher affinity for binding IgG than NK cells from 158FV or 158FF donors, so the 158F and 158V variants have respectively been designated the low and high binding affinity alleles. A gene-dosage effect was also found, with the NK cells from 158FV heterozygotes showing intermediate levels of IgG binding.

These results indicate a functional significance of the FcγRIIIA F158V transition which may have implications for the aetiology of autoimmune diseases. Association has been reported between the homozygosity for the low binding variant of FcγRIIIA (158FF) and susceptibility to systemic lupus erythematosus (SLE) in white people and Hispanic subjects, although this was not confirmed in Korean and Japanese people.

A recent study of this polymorphism in white people with RA found a weak positive association with the 158V allele, and an overrepresentation of 158VV homozygotes (odds ratio (OR)=1.6, p<0.05). Conversely, a Spanish study reported an overrepresentation of the 158FF phenotype in patients with RA. No association was found in Japanese patients with RA. To further investigate any association between this FcγRIIIA polymorphism and RA, we have analysed its distribution in two ethnically diverse populations: a large group of white United Kingdom people and a northern Indian sample.

**Abbreviations:** ADCC, antibody dependent cytotoxicity; CI, confidence interval; F, phenylalanine; FcγRIIA, Fcγ receptor IIIA; ICA, immune complex mediated arthritis; IL2, interleukin-2; NK, natural killer; OR, odds ratio; PCR–RFLP, polymerase chain reaction restriction fragment length polymorphism; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, relative risk; SLE, systemic lupus erythematosus; V, valine

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PATIENTS AND METHODS
Genomic DNA was obtained from samples of peripheral venous blood from 398 white patients from the United Kingdom with RA (Nuffield Orthopaedic Centre, Oxford, UK) and 289 ethnically matched healthy controls (Oxford Regional Transfusion Centre), and from 63 patients with RA and 93 ethnically matched controls from Uttar Pradesh, northern India. All patients with RA satisfied the 1987 revised American Rheumatism Association criteria.

An experimental review of the published methods for typing the 559T/G polymorphism disclosed a high error rate in genotyping (over 10%), mainly due to the existence of the RIIIA gene which at position 559 has an invariant G (158V) allele. To ensure unequivocal results, a method of Lathrop was used. This study had 90% statistical power to detect a genotypic relative risk (RR) of 1.6 and a significant allelic association with an OR=1.4 in the white group. The method of Lathrop.

Testing polymorphisms in candidate genes across different ethnic groups is potentially a rigorous method for identifying relevant genetic influences. Studies on FcγRIIIA have now been undertaken in RA in white patients from the United Kingdom, and Indian, Spanish, and Japanese patients. If similar associations had been found in these different racial groups there would be strong evidence of a causal relationship with the FcγRIIIA gene. However, results from this study do not support an association between the 158VV FcγRIIIA phenotype and RA. They are in agreement with the negative finding from a smaller study of Japanese patients with RA. A comparison of the published frequencies of this polymorphism among healthy controls in various populations has disclosed significant discrepancies among the published studies, most of which have analysed samples of between 100 and 200 people. The allelic and genotypic frequencies obtained in the northern Indian group were 35% versus 34% in the United Kingdom group and 28% versus 33% in the Indian group. In the Indian group, the frequency of the 158V allele was non-significantly reduced among the patients and the proportion of the 158VV homozygotes was also correspondingly non-significantly reduced (table 1). However, as there have been reports of a gene-dosage effect in this polymorphism, we analysed the RR for 158VV compared with that of 158FV or 158FF. A moderate protective effect from 158VV was found among the northern Indian patients with RA (RR=0.2; p=0.02; 95% confidence interval (95% CI) (0.04 to 0.9); table 2). The genotypic frequencies did not differ significantly in the United Kingdom group, although the proportion of 158VV homozygotes was slightly higher among the patients.

DISCUSSION
Testing polymorphisms in candidate genes across different ethnic groups is potentially a rigorous method for identifying relevant genetic influences. Studies on FcγRIIIA have now been undertaken in RA in white patients from the United Kingdom, and Indian, Spanish, and Japanese patients. If similar associations had been found in these different racial groups there would be strong evidence of a causal relationship with the FcγRIIIA gene. However, results from this study do not support an association between the 158VV FcγRIIIA phenotype and RA. They are in agreement with the negative finding from a smaller study of Japanese patients with RA. A comparison of the published frequencies of this polymorphism among healthy controls in various populations has disclosed significant discrepancies among the published studies, most of which have analysed samples of between 100 and 200 people. The allelic and genotypic frequencies obtained in the northern Indian group were 35% versus 34% in the United Kingdom group and 28% versus 33% in the Indian group. In the Indian group, the frequency of the 158V allele was non-significantly reduced among the patients and the proportion of the 158VV homozygotes was also correspondingly non-significantly reduced (table 1). However, as there have been reports of a gene-dosage effect in this polymorphism, we analysed the RR for 158VV compared with that of 158FV or 158FF. A moderate protective effect from 158VV was found among the northern Indian patients with RA (RR=0.2; p=0.02; 95% confidence interval (95% CI) (0.04 to 0.9); table 2). The genotypic frequencies did not differ significantly in the United Kingdom group, although the proportion of 158VV homozygotes was slightly higher among the patients.

RESULTS
The distributions of the FcγRIIIA 158F and 158V alleles between the patients with RA and the controls were similar in both the United Kingdom and Indian groups. The frequencies of the V allele in patients compared with controls were 35% versus 34% in the United Kingdom group and 28% versus 33% in the Indian group. In the Indian group, the frequency of the 158V allele was non-significantly reduced among the patients and the proportion of the 158VV homozygotes was also correspondingly non-significantly reduced (table 1). However, as there have been reports of a gene-dosage effect in this polymorphism, we analysed the RR for 158VV compared with that of 158FV or 158FF. A moderate protective effect from 158VV was found among the northern Indian patients with RA (RR=0.2; p=0.02; 95% confidence interval (95% CI) (0.04 to 0.9); table 2). The genotypic frequencies did not differ significantly in the United Kingdom group, although the proportion of 158VV homozygotes was slightly higher among the patients.

### Table 1
Distribution of the genotype frequencies of the FcγRIIIA 158F/V polymorphism among the patients with RA and controls in the United Kingdom and Indian groups

<table>
<thead>
<tr>
<th>Genotype</th>
<th>United Kingdom (n=420)</th>
<th>Controls (n=420)</th>
<th>χ²</th>
<th>RR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>158FF</td>
<td>281 (67%)</td>
<td>172 (41%)</td>
<td>0.01</td>
<td>1.0</td>
<td>0.7 to 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>158FV</td>
<td>139 (33%)</td>
<td>213 (51%)</td>
<td>0.71</td>
<td>1.1</td>
<td>0.9 to 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>158VV</td>
<td>9</td>
<td>35 (8%)</td>
<td>0.1</td>
<td>1.1</td>
<td>0.7 to 1.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2
Assessing the relative risk for carrying two V alleles compared with one or no V alleles

<table>
<thead>
<tr>
<th>Genotype</th>
<th>United Kingdom</th>
<th>Controls</th>
<th>χ²</th>
<th>RR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>158FF/158F</td>
<td>385 (92%)</td>
<td>35 (8%)</td>
<td>2.6</td>
<td>1.5</td>
<td>0.9 to 2.4</td>
<td>0.1</td>
</tr>
<tr>
<td>158FV</td>
<td>385 (92%)</td>
<td>35 (8%)</td>
<td>1.3</td>
<td>0.7</td>
<td>0.4 to 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>158VV</td>
<td>2 (3%)</td>
<td>14 (15%)</td>
<td>3.5</td>
<td>0.3</td>
<td>0.1 to 1.1</td>
<td>&lt;0.06</td>
</tr>
</tbody>
</table>

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white United Kingdom group is misleading. The protective effect of the 158VV phenotype found in the Indians with RA in our study reached statistical significance but it is also likely to be spurious as it was not found in the other groups and the sample studied was small.

One possible explanation for the discrepancies in the results reported so far is that one of the other neighbouring FcγR genes (FcγRI or FcγRII) is the true disease susceptibility locus. Incomplete linkage disequilibrium between the 158FV polymorphism and the actual RA predisposing allele could account for different associations in different ethnic groups.

Another significant factor influencing the activity of FcγRIIIA is its density on the cell surface, as aggregation of FcγR triggers cell activation. A study of a mouse model of immune complex mediated arthritis (ICA) has shown an interdependence between the degree of joint inflammation and cartilage destruction and the levels of FcγRIIIA expression on synovial macrophages. If FcγRIIIA is a true RA susceptibility factor, then the regions regulating gene expression, rather than polymorphisms of the coding sequence, may harbour the genetic elements for its involvement in the cause of disease. Furthermore, the signalling function of FcγRIIIA is mediated by two closely related intracytoplasmic subunits: the ζ chain of the T cell receptor and the γ chain of the IgE receptor. Comparison of the abilities of these two subunits in mediating activation signals showed that the cross linking of FcγRIIIA associated with a γ chain was significantly more efficient in signal transduction and phagocytosis than signalling through a ζ subunit. Genes for the γ and ζ subunits map to the same region of chromosome 1q as the Fcγ receptor cluster. It is conceivable that a potential polymorphism predisposing to RA in one of these two subunits may be reflected by the differential findings of genetic associations between RA and the FcγRIIIA.

Further studies of the genes in linkage disequilibrium with this polymorphism in large samples of genetically diverse populations could clarify the involvement of the IgG receptors in the cause of RA.

References

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Because none of the classification criteria
• Classification criteria can be used for diag-
that:
• Classification criteria can be used for diag-

the classification criteria proposed for that
disease. Diagnosis is an often com-
mum the possibility of including false
positive controls, but without an excessive
loss of sensitivity, which might result in
the exclusion of large numbers of true
patients.

The only objective method to derive
classification criteria is to evaluate, in a series
of patients with a given disease and in normal
controls, the sensitivity/specificity ratio of dif-
ferent diagnostic tools for that disease, and
then to select the combination of these which
shows the highest accuracy in correctly
classifying cases. Patients and controls should
have been preliminary diagnosed on the basis
of a “gold standard”. Because for the systemic
rheumatic diseases a “gold standard” does not
exist, the only standard, which can be
adopted, is the clinical diagnosis made by an
experienced specialist. This in fact was the
procedure adopted by the American College of
Rheumatology to define the classification cri-
tera for rheumatoid arthritis and by the
European Community Group to define and
validate those for SS. This method is natu-
rally far from perfect, because the pre-
definition of the groups of true patients and
true controls will invariably be influenced by
the clinical data which are still available at the
moment of the preliminary evaluation and
selection of cases. The fact that in our study the numbers of patients and controls were quite large and
were collected from different centres in
different countries nevertheless offers some
assurance that any bias in the selection proc-
есс would have been extremely diluted, and
that the entire disease spectrum was covered.
Despite these well known limitations, this
method remains the only satisfactory one
for defining and validating classification
criteria.

The only alternative is to establish classifi-
cation criteria based on the suggestions of a
group of experts. However, these criteria
would still have to be validated in clinically
defined groups of patients and controls in
order to determine their sensitivity and
specificity.

In any case, once populations of “true
patients” and “true controls” have been se-
lected, the definition of a classification criteria
set becomes a purely statistical operation—that
is, one of choosing a set of diagnostic tests and
finding the combination which shows the best
sensitivity/specificity ratio.

If these points are kept in mind, most of the
considerations in the US-European classifi-
cation criteria for SS fall to the ground. The
definitions of item III (ocular involvement)
and item V (salivary gland involvement) as
the presence of a positive test, and that of
definition was the presence of a
focus score = 1, are not merely definitions
suggested by an expert committee. They were,
on the contrary, arrived at after rigorous
statistical analysis of a large series of patients
and controls, and by testing the sensitivity/
specificity ratio of all the possible items and
combinations thereof. Moreover, the applica-
tion of a purely statistical procedure guaran-
tees that completely interdependent variables
were excluded by the procedure itself. There
are many data indicating that autoantibody
production and lymphocyte infiltration in the
minor salivary glands are related, but statisti-
cally speaking the inclusion of both items in
the classification criteria improved the per-
formance of the whole set, with respect to their
mutual exclusion. The inclusion of classification
items (items I and II) allows the researcher to start with a simple
questionnaire in selecting potential patients with SS, a point which is of great interest for epidemiological surveys. On the other hand, I would entirely agree that a limited number of patients with SS deny having any
symptoms. To avoid this misclassification of these symptomless patients, the US-European Consensus Group tested and added
an additional criterion for primary SS—

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Italy

MATTERS ARISING

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Classification criteria for Sjögren’s syndrome

I read with great interest the editorial by R Manthorpe published in the June issue of the
Annals of the Rheumatic Diseases. The author reviewed the different criteria that have been
proposed for the classification of patients with Sjögren’s syndrome (SS) and, in particular,
commented on the US-European Consensus Group criteria, which were reported for the
first time in this same issue. As the first author of the paper, I would like to discuss certain points and criticisms which he raised about our criteria set. First of all I would like to
discuss briefly the meaning of “classification criteria” and the methods by which the
European and US-European criteria for SS were derived.

Classification criteria are not meant to be used for diagnosis. Diagnosis is an often com-
plex process by which a doctor arrives at the suspicion of a specific disease in a given
patient, and then must collect enough clinical data to confirm that suspicion. Classification
criteria, on the other hand, represent a tool for research and communication, providing uni-
form criteria for the scientific community to classify patients with the same disease, select
patients for clinical-therapeutic trials, and make the data obtained by different research-
ers in different series of patients comparable. As any experienced rheumatologist knows, it is
not uncommon to diagnose a specific rheu-
matid disease in a patient who does not meet the
classification criteria proposed for that
disease.

Given these considerations we can argue that:

• Classification criteria can be used for diag-
nostic purposes only when they have a sen-
sitivity and specificity of 100%.

• Because none of the classification criteria for systemic rheumatic diseases reach this
level of sensitivity and specificity, it is evident that some patients with a given
disease will fail to be classified as having it, and some normal controls may be errone-
ously classified as patients with that disor-

Given the purpose of classification criteria, it is preferable to adopt criteria with a
specificity approaching the optimum (100%), which would reduce to a mini-

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One important factor of the Japanese III criteria is that they do not operate with or include subjective symptoms because their statistical calculations showed that it did not improve their results. This is in contrast with the US-Eur consensus group which continues to include ocular (item 1) and oral (item III) dry symptoms—unchanged from 1993. Research has shown that even though the cornea is the most densely innervated organ, there are no nerves which can register dryness. To include dry eyes in the criteria is therefore inappropriate. (Dry eyes is an iatrogenic expression which some patients are very quick to adopt.)

Another important contrast between the US-Eur consensus group and the Japanese expert group is that the latter requires at least two abnormal ocular tests for the function of the lachrymal gland to confirm the diagnosis keratoconjunctivitis sicca and two abnormal oral tests for the function of the salivary glands to confirm the diagnosis stomatitis sicca. However, sialography can stand alone. The US-Eur group requires only one test, which in practice is an abnormal Schirmer-I test (<5 mm in 5 minutes performed without anaesthesia and with closed eyes) for the lachrymal gland and an abnormal unstimulated whole saliva test (<15 ml in 15 minutes performed without tobacco, eating, and drinking during the preceding two hours) for the salivary gland. (It is usually customary to get a “confirmatory” test result when the findings are abnormal, as in HIV.) In the leader I expressed concern about the proposal that three positive results out of four objective items in an asymptomatic patient should automatically be classified as “definite” SS. If the abnormal items are IV, V, and VI, there is no proof that the lachrymal gland is also affected. Probably the greatest “negative” scientific point of discussion was the lack of comments on the observation previously published in this journal that the number of cigarettes smoked per week may have a tremendous effect on the result of the focus score in lower lip biopsy (item IV) as well as on the level of anti-SSA/B autoantibodies (item VI). In historical non-smokers the results in item IV and VI were statistically significant compared with those found in present and/or past smokers. In the last group it does not matter if the date at which they stopped was recent or several years (decades) previously. The smoking effect was highly dose dependent, with the threshold around 21 cigarettes a week. Consider the number of people with irritation of the eyes and dryness in the mouth who are have been smokers and thus might not fulfil item IV or item VI of the US-Eur consensus group. If they nevertheless have at least two abnormal functional test results from both the lachrymal and the salivary glands, I find it today medically, ethically, and morally wrong not to accept that these patients have primary SS. If research in the autoimmune/immunity/tobacco area seems only to be in its infancy.

In conclusion, I cannot advise colleagues to start using the US-Eur consensus group criteria for SS. The step towards obtaining long lasting international SS criteria was taken at the VIII International SS Symposium in Kanazawa, Japan 2002, when great acclamation was given to a proposal to form a big international SS consensus group. It is to be hoped, that this group of SS researchers from Japan, China, Europe, and America will some day, and the sooner the better, deliver their view(s) unless we could have an earlier 100% diagnostic test in our hands——valid for smokers, ex-smokers, and “never” smokers.

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References

Etanercept treatment of rheumatoid arthritis in the “real world”

A recent paper in the Annals of the Rheumatic Diseases attempted to examine the “real world” experience of etanercept treatment by comparing the incidence of disease modifying antirheumatic drug (DMARD) treatment in RA increases with the length of time the patient has been receiving the drug and that a number of these withdrawals relate to loss of efficacy. Therefore, it is reasonable to assume that the number of disease flares will increase the longer a patient with RA is receiving treatment, particularly if that treatment is failing to control the disease activity. The fact that treatment of this cohort of patients with RA had been changed to etanercept suggests that their current DMARD treatment was failing to control their disease. Therefore it is likely that there would be an increased number of disease flares in this group before starting etanercept treatment. Although not stated in the paper, it is reasonable to assume that this cohort of patients with RA had been receiving their previous DMARD treatment for some time before changing to etanercept treatment. Therefore what the authors of this paper have compared is the number of RA disease flares in a cohort of patients with RA in their first year of etanercept treatment with the number of RA flares in their last year (failing) DMARD treatment. The results are predictably in favour of the new treatment.

Would the authors have found the same results in future that they had conducted a “fairer” comparison and compared the number of disease flares in this RA cohort during their first year of the previous DMARD treatment, especially if it was methotrexate, with the first year of etanercept treatment?
Also, the very nature of the American College of Rheumatology “response” criteria is such that no absolute value is sought to demonstrate a treatment’s success, but rather it is the individual subject’s relative improvement compared with his or her baseline assessment. If Dr Smith’s assumption was made, this method would also be invalid.

Our design attempted to mimic these criteria in a “real world” situation. Although we agree that some bias was introduced by our design, we would also argue that in order to use subjects as their own controls, their overall status must be the same between the two periods of comparison. Comparing outcomes within the same subject during the first years of a new DMARD would eliminate the presumed problem introduced by Dr Smith’s comments, while potentially introducing others.

A more ideal study would be to compare outcomes (that is, flares) between two groups of patients with RA exposed to the same DMARD and matched for multiple variables, including disease duration, number of DMARDs previously used, similar comorbidity, etc. However, this would eliminate the “real world” setting.

We thank Dr Smith for his interest in our recent publication. In his comments he states that it is well documented that the withdrawal rate from disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) treatment is increased with increasing duration of use. He therefore suggests that our study design biases our results because by using patients who have changed their DMARD, we have selected those for whom the usefulness of that particular drug has been outlived. However, we contend that although the withdrawal rate from DMARDs increases with time, this may be a consequence of increasing disease severity and RA refractoriness, and not simply lost effectiveness of the drug.

The natural history of RA as a progressive and increasingly recalcitrant disease is also well documented. Furthermore, recent studies have shown better outcomes when DMARDs are introduced to naïve patients, suggesting that those who have already been exposed to other DMARDs are even more difficult to control. Also, the very nature of the American College of Rheumatology “response” criteria is such that no absolute value is sought to demonstrate a treatment’s success, but rather it is the individual subject’s relative improvement compared with his or her baseline assessment. If Dr Smith’s assumption was made, this method would also be invalid.

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References

Authors’ reply
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