The Journal of Immunology

# Comment on ''Functional Analysis of a Complement Polymorphism (rs17611) Associated with Rheumatoid Arthritis''

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*J Immunol* 2015; 195:3-4; ;
doi: 10.4049/jimmunol.1500822
http://www.jimmunol.org/content/195/1/3



*The Journal of Immunology* is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

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# Comment on "Functional Analysis of a Complement Polymorphism (rs17611) Associated with Rheumatoid Arthritis"

In their published article, Giles et al. (1) explored functional consequences of rs17611 in the TRAF1-C5 region and propose a mechanism for its contribution to rheumatoid arthritis (RA) pathology, as this SNP would associate with RA. To substantiate the claim that the SNP associates with RA, the authors referred to the following studies: Refs. 2 and 3.

However, the data presented by Kurreeman et al. do not indicate a significant association ($p = 0.19$) in 544 subjects (Ref. 2, see Table I). In addition, haplotype block analyses of this risk locus shows that block 2 is significantly associated with RA, while block 3 (which includes rs17611) is not (Ref. 2, see Fig. 1). Similar data by Plenge et al. (3) across 3372 subjects support this lack of association. Recent genome-wide association studies data across 55,000 European subjects (4) provide accurate estimations of risk across hundreds of SNPs in this locus. Again, no signal of association for rs17611 has been demonstrated in the available published datasets originating from this study (Fig. 1), which also shows that rs17611 is in relatively low linkage disequilibrium (LD) with the lead SNP rs10985070 ($r^2 = 0.4$). Moreover, independent secondary association signals were not observed in the TRAF1-C5 locus in a study by Eyre et al. (5), excluding the possibility that rs17611 could represent a second hit at this locus.

On the basis of the published genetic data, we believe caution should be taken in implicating the effects of rs17611 in relation to the immunological mechanism underlying the genetic risk of TRAF1-C5 to RA.

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Abbreviations used in this article: LD, linkage disequilibrium; RA, rheumatoid arthritis.

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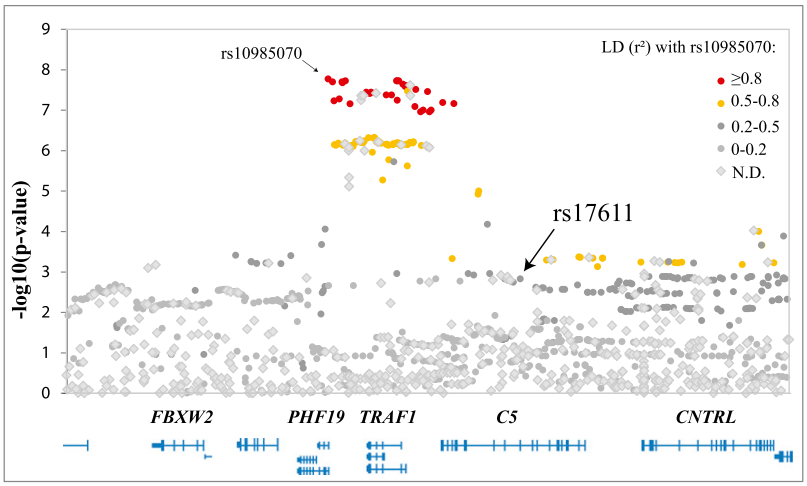


**FIGURE 1.** Regional association plot for the TRAF1-C5 region. The *x*-axis shows the chromosomal position of the all queried SNPs located on chromosome 9p33p34 over a region of 500 kb. The *y*-axis displays the –log10 (*p* value) of associations with RA. The *p* values were a result of analysis on the European population as part of the Okada et al. paper (4): 14,361 RA cases and 43,923 controls from 18 studies of Europeans descent. Pairwise LD values ($r^2$) were calculated from individuals of the 1000 Genomes Project (CEU) relative to the highest associating SNP rs10985070 using SNAP (6). N.D., LD for SNP is not determined.

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www.jimmunol.org/cgi/doi/10.4049/jimmunol.1500822

# Response to Comment on "Functional Analysis of a Complement Polymorphism (rs17611) Associated with Rheumatoid Arthritis"

In their *Comment*, Messemaker et al. discuss genetic data that show that block 2 within the TRAF1-C5 locus is a risk for rheumatoid arthritis (RA), while block 3 is not associated. We acknowledge these data, which illustrate that, when taken in isolation, block 3 does not impact disease risk. It is clear that the genetic data are robust (1); however, there is no question that the rs17611 single nucleotide polymorphism (SNP) in C5 results in an amino acid change in C5 that alters its rate of cleavage by elastase: an enzyme present at high levels in neutrophil-driven or neutrophil-associated diseases such as RA. We believe that it would be important and interesting to further analyze whether this functional polymorphism in block 3, which affects the proinflammatory capacity of C5, has any impact on the risk haplotype in block 2. While genome-wide association studies have identified a number of independent secondary association signals, these are not exclusive (2); the strong functional data that we demonstrate with the C5-V802I variant suggest that potential interactions should be specifically tested in future studies to confirm or exclude them.

In our article (3), we reference other papers where the specific rs17611 SNP has been linked to different diseases. Chai et al. (4) show an association ($p < 0.007$) of rs17611 (and its linked set) with periodontal disease; Woehrl et al. (5) show an association ($p < 0.002$) of rs17611 with outcome in pneumococcal meningitis; Hoke et al. (6) show an association ($p < 0.01$) of rs17611 with adverse cardiovascular outcome; and Greisenegger et al. (7) show an association ($p < 0.005$) of rs17611 with risk for ischemic stroke. Together, these linkages provided a strong rationale to explore the functional consequences of the rs17611 SNP on C5 activities, the major focus of our paper.

First, we show that the rs17611 SNP is associated with clear differences in C5 turnover and elevated levels of the proinflammatory product C5a in healthy individuals and RA patients; our finding warrants further investigation of the impact of this polymorphism on risk associated with block 2. We go on to define the mechanism by which the single amino acid change provokes these differences. The genetic data do not detract from the importance of our demonstration that the polymorphism impacts C5 turnover and increases plasma levels of the proinflammatory molecule C5a, and of our description of the atypical route by which this is achieved (3).

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Abbreviations used in this article: RA, rheumatoid arthritis; SNP, single nucleotide polymorphism.

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