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AUTHOR CONTRIBUTIONS

D.v.d.W. performed the ELISA assays, performed statistical analyses, produced the figures, **Supplementary Table 1** and **Supplementary Note** and wrote the paper. W.G.A. performed statistical analyses. W.V. performed the *HLA-DRB1* genotyping. R.R.P.d.V. supervised statistical analyses. J.J.H.-D. performed and supervised statistical analyses. T.W.J.H. contributed to the design of the study and the writing of the paper. R.E.M.T. designed the study, supervised the laboratory experiments and contributed to the writing of the paper. All authors contributed to the final paper.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Lundberg *et al.* reply:

We recently reported that *HLA-DRB1* shared epitope alleles, *PTPN22* and cigarette smoking, all well-known risk factors for CCP-positive rheumatoid arthritis, in fact mainly constitute risk factors for the subset of CCP-positive rheumatoid arthritis subjects that also have antibodies to citrullinated α-enolase peptide-1 (CEP-1), the immunodominant β-cell epitope of citrullinated α-enolase[1]. We thank van der Woude *et al.*[2] for their response to our publication. Van der Woude *et al.*[2] use an independent cohort of individuals with rheumatoid arthritis in a case-only analysis and demonstrate a strong association of *HLA-DRB1* shared epitope alleles and smoking with the subset of anti-CCP–positive cases that also have antibodies to a citrullinated vimentin peptide[2]. However, only a marginal association was found with antibodies to a peptide derived from citrullinated fibrinogen. The findings of van der Woude *et al.*[2] thus complement the findings of our study[1], as well as those of our previous studies[3,4], that antibodies to specific citrulline-bearing epitopes on defined physiological antigens are present in different subsets of rheumatoid arthritis. Furthermore, in our previous studies[3,4], cross-absorption experiments showed limited cross-reactivity of antibodies to CEP-1 with other citrullinated antigens. Therefore, the data from Van der Woude *et al.*[2] provide further support for our suggestion that these antibodies can be used to subgroup anti-CCP–positive rheumatoid arthritis cases and thus reveal etiological differences in various subsets of the disease. The fact that immunity to some citrullinated antigens (α-enolase and vimentin derived) but not others (such as the fibrinogen-derived peptide studied by van der Woude *et al.*[2]) associates strongly with both smoking and *HLA-DR* shared epitope alleles is in line with our hypothesis that smoking may induce citrullination of certain proteins in the lungs and that immunity to these post-translationally modified proteins may be determined by certain *HLA-DR* alleles[5].

In light of the study of Van der Woude *et al.*[2], it will be of great interest to dissect these rheumatoid arthritis subsets further, such as those subsets concordant and discordant for anti-citrullinated vimentin and anti-citrullinated α-enolase antibodies. We are currently examining these and other subsets in EIRA, a Swedish population-based case-control study[6]. In addition, there are many other potential citrullinated autoantigens awaiting investigation, and it is possible that other autoantibody specificities may be linked to smoking and *HLA-DR* alleles. It is also possible that antibodies to the citrullinated fibrinogen peptide studied by Van der Woude *et al.*[2], although not apparently associated with smoking, may identify subsets of rheumatoid arthritis associated with other etiological agents. One candidate is the periodontal pathogen *Pophyromonas gingivalis,* which has been linked to rheumatoid arthritis in a number of studies (reviewed by Lundberg *et al.*[7]). We have recently demonstrated that the deiminase produced by this organism has the capacity to generate multiple citrullinated peptides from fibrinogen, in addition to some from α-enolase[8]. Whether *P. gingivalis* infection is specifically linked to autoimmunity to citrullinated fibrinogen, α-enolase or any other subgroup of the anti-CCP response is currently under investigation.

Our study[1] was, to our knowledge, the first to demonstrate how the combination of epidemiology, genetics and autoantibody responses to specific physiological antigens can be used to investigate the etiology of defined subsets of anti-CCP–positive rheumatoid arthritis. The work of Van der Woude *et al.*[2] validates our approach and indicates the way forward in understanding how environmental agents, in the context of defined genetic variants, may trigger specific immune reactions potentially able to induce arthritis.

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