Author's response to reviews

Title: On the Wegener granulomatosis associated region on chromosome 6p21.3

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Author's response to reviews: see over
**Ad reviewer: Bobby Koeleman**

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

**Abstract and throughout the paper:**

1. *The authors speak about ‘linkage mapping’. I believe this is a consistent mix-up, because I only see association analyses in this manuscript.*

We apologize for this mix-up. Certainly we have done a population based association study. We corrected this mistake throughout the entire manuscript.

2. *The result section of the abstract gives to little information, please give names of microsatellite and SNPs (rs-numbers) and Odds-ratios and p-values for the positive associations.*

We included information on the microsatellite and SNP in addition to OR and p-values for positive results.

3. *‘by the used approach” rephrase, this is unclear.*

We rephrased the abstract and eliminated this sentence as it gives no necessary information here.

**Introduction:**

1. *“Several candidate genes…” which?*

Examples for investigated candidate genes for WG are now added in the introduction section.

2. *The microsatellite that previously found to be associated is discussed. Please give name / identity and information were it is located in respect to the other markers studied here, especially in figure 1.*
All microsatellites (MS) are described in additional file 1 by an internal number such as #1.0.3.7 (the previously associated MS), the location due to UCSC freeze May 2004 (we updated the latest freeze) and oligonucleotides used for PCR reaction, *inter alia*. The location of MS in respect to each other is also included in this file. Figure 1 rather represents an overview for quickly grasping the relative location of all markers and the gaps, where no suitable MS has been identified. In figure 1, a scale was added to demonstrate distances between markers. Furthermore, the additional information on the MS #1.0.3.7 ameliorates the figure legend.

Results:
1. *Similar to above, please relate the new results to the previously found association of the Microsatellite*

We related the results on the WG associated region obtained previously with the data found here throughout manuscript in all sections.

2. *Section “Analysis of the RXRB gene” Please give consistently p-values for significant findings (second but last sentence). P-values should be rounded up to one number after the zero’s (p=0.02 instead of 0.0159, I would except 0.016, although this also suggest a false accuracy)*

As recommended we rounded all p-values throughout the manuscript.

3. *Consistency of type of analysis: Why is only the BTNL22 variation tested with stratification for ANCA?*

We added genotyping results for the *RXRB* variation of ANCA-negative patients. Hence, table 3 has been rearranged with the new data. In the discussion, a short paragraph has been included.

4. *The paper would benefit from a LD-analysis of the marker, HLA alleles, and the previously associated microsatellite.*

As recommended, LD analyses were performed between MS #1.0.3.7, the *HLA-DPB1* alleles (data adapted from Jagiello *et al.* Hum Genet, 2004; information for allele frequencies are given in the new additional file 2) and the *RXRB rs6531* SNP. Heretofore, we created a new figure 2 which depicts the data of the LD analyses by $D'$, *LOD* and $r^2$ values graphically. These results are briefly discussed in the discussion section.
Discussion:
1. See comment 4 of the result-section. Statements are made about LD between markers, which should have been illustrated / investigated.

See comments above.

2. Second but last sentence: “which is shown to be prone to ascertain strong association”.
Unclear, please clarify.

We clarified this sentence in the discussion section.

Tables:
1. Please correct the accuracy of the reported p-values (i.e. 0.02 instead of 0.0244, 0.05 instead of 0.0487)

We corrected the accuracy of all p-values.

2. Table 3 and 4: OR’s reported are each time calculated as one category versus the grouped others. This is more a measure of association than a risk estimate. It is much more informative to simply give a p-value for each analysis, and report OR’s relative to the wild-type allele / genotype. That is: calculate OR of allele T versus C (OR of C is set at 1.0) and OR of allele A versus G (OR of G is set at 1.0).

The ORs were recalculated based on the recommendations.

Ad reviewer: Michael Frosch

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

abstract, chapter background, page 2: For the reader not familiar with the recent studies of genetic associations with WG, the selection of the 3.6MBp region for linkage mapping is not
comprehensible, even the selection of the BTNL2 gene. These selections should be explained more exactly to the reader even in the abstract.

We clarified our intention for analysing, both, the 3.6 MBp region investigated here and the BTNL2 polymorphism in the abstract and the background section.