Correspondence

The association between the CC chemokine ligand 5-28>G and tuberculosis susceptibility

To the Editor

We read with interest the article by Lu et al[1] published in this journal. In their systematic review and meta-analysis, the authors assessed the association between chemotactic chemokine (C-C motif) ligand 5 (CCL5) -28C>G polymorphism and tuberculosis (TB). The authors identified 12 articles out of which 4 were excluded because they were not relevant. The remaining 8 case-control studies were included in the review and the subsequent meta-analysis. The study concluded that there was no difference in CCL5 -28C>G genotype distribution between TB patients and controls. The studies were then subdivided by ethnicity (Asian, Arab and Caucasian), and a reduced risk was identified among Asians and Arabs.

Our first observation pertains to the stratification of patients in this study where Chinese and Indians were grouped together under a common ethnicity labeled 'Asian'. We do not feel that the 2 groups constitute a common ethnicity. Indeed one of the included studies was conducted on a single tribe in North Central India,[2] and the results may not be generalizable to the whole of Asia, or even India for that matter.

Our second, and perhaps more important observation relates to the methodology employed in this study. Systematic reviews constitute the highest quality evidence and deservedly sit at the top of the pyramid of evidence as they generally combine studies of the highest quality into one large study, and sometimes a pooled combined effect size is calculated in a meta-analysis. It is not surprising therefore that sometimes decision-making, whether at individual, institutional, regional, or even global level may be undertaken in the basis of these studies. The greater advantage of meta-analyses is increased power over the individual studies, but that should not in any way be at the expense of methodological quality. It is therefore of paramount importance, that studies selected for systematic reviews undergo vigorous methodological assessment to ensure good quality, and to include only those of high quality if the resulting meta-analysis is to be robust. The authors did check for heterogeneity and publication bias. The latter is essentially almost unavoidable as some small or negative studies are bound to go unpublished. Assessment of the methodological quality of included studies, however, is even more important, which the authors did not state clearly. Case control studies are particularly prone to selection bias, and this needs to be checked for, and explicitly stated in the methodology section.

Thirdly, we would like to express our concern that both of the Arabic studies included in the meta-analysis[3,4] actually reported increased risk of TB with the stated polymorphism, we therefore do not see how combining those 2 studies in a Forrest plot suddenly changes this risk in the opposite direction. It is not clear why the events reverse when the subgroup analysis was performed. In Ben-Selma et al's[3] study for instance, in the Forrest plots in Figures 2B: 21 cases versus 10 controls in Figure 2B becomes 80 cases versus 90 controls in Figure 3. This paradox can be seen more clearly in Selvaraj et al[5] where none of the cases and controls in Figure 2B had any events, while all of the cases and controls had events in Figure 3. The meta-analysis in Figure 3 is a subgroup analysis of Figure 2B, and should presumably have similar number of events for individual subgroups.

Finally, we do not see what further new information this meta-analysis adds to the previously published meta-analysis[6] besides 2 presumably unpublished university dissertations, each of which seems to have been conducted by only one person (References 25 and 26 in the meta-analysis). This may well have eliminated publication bias, but again, methodological quality assessment of these 2 crucially detrimental studies is not clearly stated.

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Reply from the Author

We gratefully acknowledge the comments of Dr. Adwan. On his third question, we will look into this and check the data carefully. If the data input is wrong which can affect the whole conclusion, we will double check the statistics, and submit the amendments in due time.

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doi: 10.15537/smj.2016.1.14223