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# Reply to Daly and Rioux response

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We agree with most of the points raised by Daly *et al* in their response to our letter. However, we have some further remarks.

Firstly, there are a number of explanations for the observed heterogeneity across the study populations. We did indeed imply that differences in allele frequencies between populations is one plausible explanation for this observation, because the estimated ORs were based on the allelic frequency in the different populations of cases and controls. The underlying reason for these differences is another issue and might be (as proposed by Daly *et al*) due to ascertainment differences between studies, unaccounted for environmental factors and differences in the proportion of females/males in the different studies. We also suggest that these differences might arise because of population-specific effects, since the 95% confidence intervals (CI) for the OR in two cohorts that show an effect (German and Canada/Italy; 95% CI are 1.16–2.03 and 1.21–3.16, respectively) do not overlap with the 95% CI for the OR in the Scottish population (95% CI is 0.62–1.16).

Secondly, another explanation for the observed heterogeneity is that the R30Q is not actually the variant influencing the phenotype. R30Q may be closely linked to the disease variant but the recombination history of each population has eroded the association in different ways.

In summary, we are in complete agreement with Daly *et al* that there is substantial heterogeneity in the populations studied, and the source of this heterogeneity will be of considerable interest to explore.

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