LETTER TO THE EDITOR

Reply: Shared environmental effects on multiple sclerosis susceptibility: conflicting evidence from twin studies

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Sir,

Dr Fagnani and co-authors propose a further investigation of whether differences in results between their study (Ristori et al., 2006) and ours (Westerlind et al., 2014) are due to methodological or biological differences (Fagnani et al., 2014). We agree that potential differences are an important issue, but would argue that in this case, it is a matter of interpretation of the results.

In the original Italian study (Ristori et al., 2006), based on a data collection at 73 multiple sclerosis clinics in Italy over 5 years, Ristori et al. (2006) identified 347 twins with multiple sclerosis. Of these, 129 declined study participation, citing not being twins, and an additional 25 individuals could not be contacted and were thus excluded. The rate of excess ascertainment (37%) was higher than that due to methodological issues present in the Italian twin registry (12%) (Salvetti 1997).

Of the remaining twins, Ristori et al. (2006) identified 59 monozygotic and 157 dizygotic pairs, giving probandwise concordance rates of 15.6% and 3.7%, respectively. Fagnani et al. (2014) write in their letter that the monozygotic concordance rate corresponds to that which presented in Brain, whereas the dizygotic concordance rate of 3.7% differs from our 1.7%. We do not agree with this statement, as the 95% confidence intervals (CI) presented in the original Italian study (0.8–6.6) clearly overlap with our observation. In both studies, the low prevalence of multiple sclerosis leaves twin studies lacking power. We observed four dizygotic twins out of 237 to be concordant. If we had observed one more concordant pair, our concordance estimate would have been 2.5%. In the Italian sample six dizygotic twins out of 157 were concordant; likewise, if one less pair would have been observed concordant it would also have resulted in a concordance rate of 2.5%. Thus the difference discussed would be non-existent if only one dizygotic twin in each sample were misclassified in disease status, or one pair in each sample were misclassified in zygosity. Observing that such a small change, well within the error margin, renders our estimates similar, we believe that the observed difference should be interpreted with caution.

Furthermore, Fagnani et al. (2014) write that the results from the heritability estimates from the program Mx differ. In the Italian study the genetic component was estimated to 0.48, shared environment to 0.29 and non-shared to 0.23. Again, the point estimates are different, as the Swedish turned out to be 0.64, 0.01 and 0.35, but if we include the confidence intervals reported in both the Italian and the Swedish study, there is no significant difference between the estimates because confidence intervals again overlap. The genetic component estimated in Italy had a CI ranging from 0.06–0.86 and for the shared environment; the CI was 0.00–0.60. The CI for the Swedish shared environment estimate was 0.00–0.18.

Although we cannot rule out country-specific multiple sclerosis heterogeneity, the differences between our results and those of...
Fagnani et al. (2014) seem to be negligible. We conclude that our heritability analysis is well in line with previous results.

References


