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LETTER TO THE EDITOR

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

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Sir,

We read with interest the paper by Westerlind *et al.* (2014) on the familial risk in multiple sclerosis. They applied an extended family design to estimate familial risks for multiple sclerosis, and used a twin approach to quantify the contributions of genetic and environmental factors in shaping individual susceptibility to the disease. The correlations in susceptibility of monozygotic (MZ) and dizygotic (DZ) twins ('tetrachoric correlations' under the 'liability-threshold' model, which provide information on magnitude of genetic and environmental components; Neale and Cardon, 1992) disconfirmed shared environmental effects, in favour of genetic and unshared (individual-specific) environmental influences in Sweden: the biometric model provided a zero estimate for the shared environmental component, a heritability of 0.64 and an individual-specific environmental component of 0.36. These estimates did not change after using an extended twin-sib model and incorporating data from additional non-twin siblings and half-siblings. The authors conclude that these results reflect the proportion of heritable and non-heritable components in multiple sclerosis risk and attribute differences from published findings to previous study samples being not representative of the examined population.

In Italy, where the world's largest twin registry is potentially available (Salvetti *et al.*, 1997), we had the opportunity not only to ascertain all patients and all twins in a population that approaches 60 000 000 inhabitants, but also to directly compare areas of medium (continental Italy) and high multiple sclerosis prevalence (Sardinia). We cross-linked the database of 73 multiple sclerosis clinics (uniformly distributed throughout Italy) and that of the Italian Multiple Sclerosis Society (AISM) with the Italian Twin Registry (Stazi *et al.*, 2002), virtually ascertaining all Italian twins with multiple sclerosis (Ristori *et al.*, 2006). Proband-wise concordance in Italian monozygotic twins was comparable with that reported for Swedish monozygotic twins (15.6% versus 15.3%), whereas proband-wise concordance for dizygotic twins was higher in our study (3.7% versus 1.7%). The estimated tetrachoric correlations for multiple sclerosis in Italy were quite different: the contribution of shared environment was 0.29, meaning that this component may explain around one-third of the variance in liability to multiple sclerosis; our heritability estimate was 0.48, and the contribution of unshared environment was 0.23.

The stronger heritable component found by Westerlind *et al.* (2014) may be compatible with the higher multiple sclerosis prevalence in Sweden compared to Italy, which may partially reflect a larger degree of genetic penetrance. Of note is the negligible role of shared environment found in the Swedish study that contrasts with the widely accepted notion (confirmed in the co-twin control section of our study) that early exposure to risk factors is relevant for disease development (Handel *et al.*, 2010). As our study avoided ascertainment limitations, we think that components of heterogeneity cannot be excluded at population level in the cause of multiple sclerosis. Given the implications that these studies

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have, in particular for gene mapping efforts, it is important to keep an open mind about differences that may be biologically relevant rather than simply methodological.

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