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Lack of support for association between the KIF1B rs10492972[C] variant and multiple sclerosis

International Multiple Sclerosis Genetics Consortium (IMSGC)

To the Editor

In their recent communication, Aulchenko et al.[1] suggested that the rs10492972[C] variant of KIF1B increases susceptibility to multiple sclerosis. In an attempt to replicate this observation, we genotyped this variant in eight case-control and three trio-family collections (in total 22,854 individuals were considered, comprising 8,391 cases, 8,052 unrelated controls and 2,137 trio families). None of these studies showed evidence for a statistically significant association; more than half of the studies showed a trend in the opposite direction (Fig. 1). Based on the odds ratio (OR) reported by Aulchenko et al.[1] (OR = 1.35), each of the collections we studied had >80% power to demonstrate association at the 5% significance level, except for the two smaller Australian studies; a population where association with this KIF1B variant has already essentially been excluded[2]. We also found no evidence for association with rs10492972[C] in analyses that considered all of our data together or those that pooled our new data with the allele counts reported by Aulchenko et al.[1] (final P = 0.1). Given the P value originally reported by Aulchenko et al.[1] ($P = 2.5 \times 10^{-10}$), it is important to consider why this association has not been replicated.

The genesis of the original claim for association is important. The genome-wide association study performed by Aulchenko et al.[1] was predicated on the notion that in a small genetically isolated population, risk alleles that are rare in the general population may have become concentrated and thereby can be more readily detected. However, there was limited power in using this approach due to the small sample size (45 cases and 195 controls), and no significant associations were identified in the initial genome-wide association study[1]. In this setting, the odds that a modestly associated variant (P = 0.0004) from a candidate gene is genuinely associated with the disease are unfavorable[3]. The possibility that perhaps this variant is relevant in The Netherlands, Sweden and Canada (the populations studied by Aulchenko et al.[1]) but not elsewhere in the world seems unlikely considering the allele frequencies we have observed. In all of the collections we tested, the observed allele frequency was comparable with that seen in the European CEU HapMap samples (frequency = 0.34). However, in the study from Aulchenko et al.[1], although all of the case groups showed a HapMap-consistent frequency for rs10492972[C], the frequency of this allele was reduced in the control groups (allele frequency in Dutch isolate controls was 0.21 and the allele frequency in pooled controls was 0.27). This is the reverse of what would be expected if the risk allele had been concentrated in the Dutch population. After testing, there is no meaningful allele frequency difference between the cases in our new data and those

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originally reported; however, a significant difference in the allele frequency between the two control groups was observed ($P = 3.5 \times 10^{-16}$).

The Swedish population is the only one considered in the original report1 that has been directly studied here. In the Swedish samples considered by Aulchenko et al.[1] (826 subjects and 997 controls), modest apparent association was reported, whereas in the nonoverlapping Swedish samples we typed (1,239 subjects and 736 controls), no association was found. Comparing these two Swedish data sets indicates that this divergence of results stems almost exclusively from a difference in allele frequency between the control groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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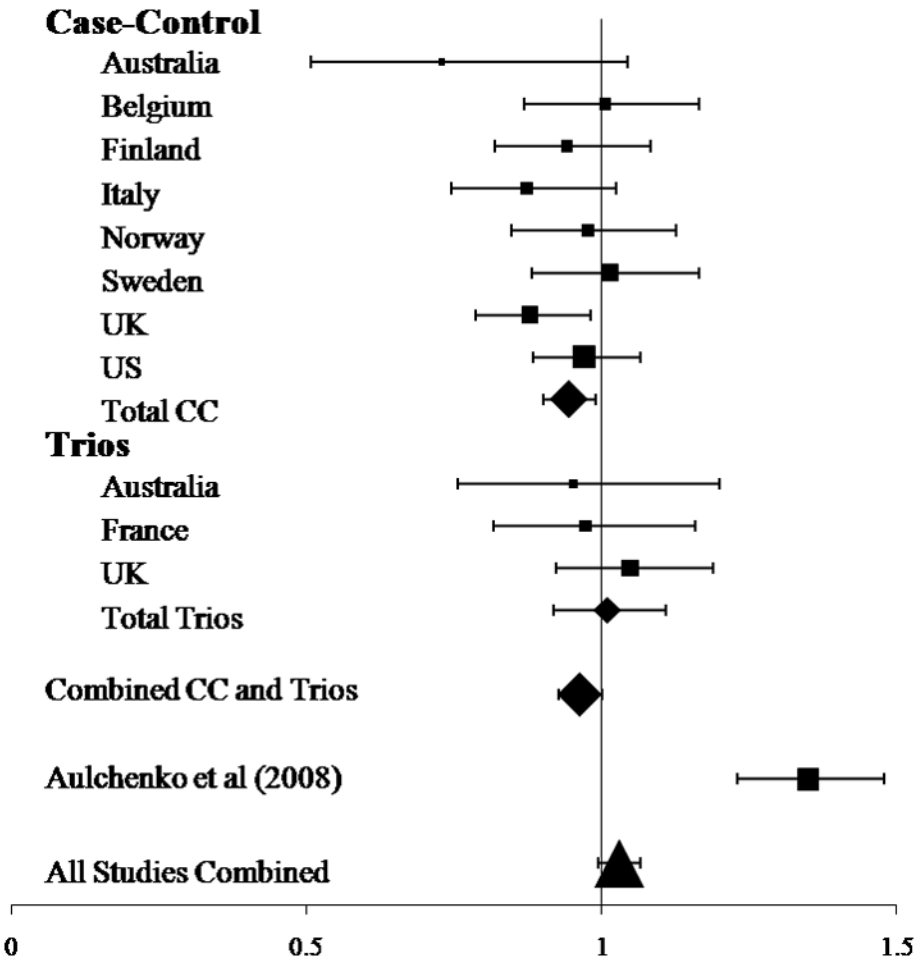

Figure 1.

Odds ratio for the rs10492972(C) allele. OR > 1.0 are consistent with the original study by Aulchenko et al.[1]. The area of the symbol is proportional to the number of cases included in the respective analysis. The error bars indicate the 95% confidence interval (see Supplementary Note for more detail regarding our new collections). Analysis was performed using PLINK[4] for the individual collections and UNPHASED[5] for the combined analyses.