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IGNG1-IGNG3 locus and its possible role in the multiple sclerosis

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Motivation and Aim: A large amount of GWAS data on multiple sclerosis (MS) has been obtained recently almost exclusively for populations dominated by Caucasians. Unfortunately, SNPs that display significant association with MS may only be linked to those that are mechanistically related to the disease development. In addition, GWAS does not provide any idea on the mechanisms of the SNP influence. Such information can obtained from eQTLs, but an eQTL also usually marks only a fairly large locus. Therefore, to study genome segments functionally associated with disease developement it is relevant to identify a rather long genome segments containing several SNPs and perform enrichment analysis for the features associated with the segment.
Methods and Algorithms: The idea of our approach is to take into account SNPs displaying low association with the target feature, and discard the corresponding genome segments, thus reducing the target regions. We have generated a set of loci enriched with SNPs associated with the MS development. Then, we created two SNP lists, statistically associated and non-associated with the development of MS according to all GWAS data. SNPs strongly linked with SNPs associated with MS were added to the target list, whereas SNPs linked with SNPs displaying low MS association were discarded. The second list contained SNPs simultaneously linked with two SNPs, statistically associated with MS according to all GWAS data set, the third list contained SNPs linked with three MS associated SNPs. Surprisingly, all SNPs in the final list were found in one locuse in chromosome 14, containing IGHG1 and IGHG3 genes and in several loci in chromosome 6 (containing HLA genes).
Results: Out of 18302 SNPs not associated with MS or linked with non-associated SNPs only 13 are very frequent in Europeans (> 0.3) and very rare in Africans and Asians (< 0.03) in population frequencies. Conversly, out of 7524 SNPs associated with MS or linked with associated SNPs 14 displayed such population frequency bias, and of these all but one were found in the locus we identified in the chr 14 or in its immediate vicinity. More to the point, the given locus is associated with IgG index (the ratio of concentrations of IgG in the cerebrospinal fluid and serum as compared with the same ratio for albumin). According to the data of (1) 5 out of 6 SNPs associated with the IgG index, are on this site
Conclusion: As for the mechanism, we propose that IgG increases antigen presentation by interacting with FcRγ-receptors (2), and stimulates B-cell secondary immune responce to IgG synthesis by activating T-helper cells of antigenic presenting complex. As it is known, the MS frequency is about ten-fold higher in countries with a predominance of the Caucasian population. In addition, the disease development sometimes is different for non-Europeans. For instance, the abnormal intrathecal synthesis of IgG, reflected by cerebrospinal fluid oligoclonal IgG bands and increased IgG index, is much less frequent in Japanese (3). We assume that the given locus is responsible for the corresponding differences. We suppose that at this locus there was a positive selection during the resettlement to the high latitudes of Europe.

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