Multiple sclerosis genetic risk burden confers earlier onset.
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Objective: To determine the contribution of the genetic risk component for multiple sclerosis (MS) on age of onset (AOO).

Background: AOO is a strong predictor of MS evolution independent of disease duration. Factors influencing AOO are not well known though HLA-DRB1*15:01 (DR2), the primary MS genetic risk factor, has been consistently associated with earlier onset.

Design/Methods: The study population included 1,076 non-Hispanic white MS cases with detailed epidemiologic and genetic information. AOO was age of first symptom indicative of MS. Genetic data for 201 putative MS risk variants were genotyped on a customized Illumina iSelect Platform by the International MS Genetics Consortium. A tagging variant for HLA-DRB1*15:01 (DR2) was available (rs3135388). AOO was natural log transformed to meet normality assumptions for linear regression models that included each risk variant (coded with respect to MS risk) as a predictor, adjusting for gender, MS subtype, birth year, education, and DR2 carrier status. A genetic risk score (GRS) was also investigated and was the sum of all alleles for the 201 variants.

Results: As expected DR2 carriers had a younger AOO. A single risk allele increase in the GRS was associated with a 0.3% decrease in AOO (p=0.0036). When we compared quantiles of the GRS distribution, those with the greatest genetic burden were 7.2% (p=0.0018) younger at onset than those in the lowest burden. On average, the predicted AOO was 3.8 years earlier for DR2 carriers with the highest GRS quantile burden (30.5 years) versus DR2 non-carriers with the lowest GRS quantile burden (34.3 years). Among the genic variants, those in CLEC16A (which regulated DR2 expression) were most associated with earlier AOO: rs12708716 (2.9% earlier per risk allele; p=0.012) and rs1985372 (2.6% earlier per risk allele; p=0.02).

Conclusions: The MS genetic risk component significantly predisposes MS susceptible individuals for earlier onset.