MS risk alleles for AHI-1 and IL22RA genes are associated with relapses in children and adults with MS

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Objective: We sought to determine whether established multiple sclerosis (MS) genetic susceptibility factors are associated with relapse rate in children and a replication cohort of adults with MS.

Methods: Genotyping was performed for 185 children with MS or clinically isolated syndrome with high risk for MS from two Pediatric MS Centers. They were prospectively followed for relapses. Fifty-two non-HLA MS susceptibility SNPs were both evaluated for association with relapse rate. Cox regression models adjusted for disease-modifying therapy (DMT) use, genetic markers of ancestry and sex. Replication of pediatric subject SNP results was performed using a second cohort of 141 adult MS subjects from the Southern Tasmanian Multiple Sclerosis Longitudinal Study.

Results: Over 622 patient-years of follow-up, 408 relapses were captured. Several non-HLA risk SNPs were associated with relapse hazard ($p< 0.05$) in the pediatric subjects. After adjustment for *HLA-DRB1*15:01*, sex, vitamin D level, and DMT, having two copies of risk allele for *AHI1* was associated with increased relapses in the pediatric subjects (HR 1.67, 95%CI 1.12-2.49, p=0.012) and this result replicated in the adult subjects (HR 1.81, 95% CI 1.07-3.08, p=0.028). The risk allele downstream of *IL22RA2* increased the hazard to relapse associated with low vitamin D in both children (HR 1.59, 95% CI 1.25,2.03, $p< 0.001$) and adults (HR 1.92, 95% CI 1.20,3.07, p=0.006).

Conclusions: Our results suggest genetic risk variants may also contribute to disease course. We further find genetic modification of vitamin D effects on relapse rate.

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