Prediction of conversion from optic neuritis to multiple sclerosis: novel application of a genetic risk score

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Optic Neuritis (ON) is a frequent first feature of multiple sclerosis (MS), but a formal diagnosis of MS may be delayed by years. The challenge is to distinguish MS-ON from other forms of ON at time of presentation. MS is heritable with numerous common genetic variants associated with disease risk. We aimed to investigate if a multiple sclerosis genetic risk score (MS-GRS) aids prediction of MS at time of diagnosis of ON as a clinically isolated syndrome (CIS).

Methods:

We studied individuals in the United Kingdom Biobank, a large longitudinal database containing phenotypic and genetic data on 500,000 individuals. We retrieved diagnoses of MS and ON from retrospective (before baseline visit) and prospective (after baseline visit) self-report, hospital, and GP records, and analysed the co-occurrence of MS and ON.

We developed the MS-GRS based on 310 single nucleotide polymorphisms (SNPs) and eight HLA alleles associated with MS risk in previous studies. We assessed the power of MS-GRS to discriminate between MS and healthy controls using receiver-operator characteristics-area under the curve (ROC-AUC). We analysed whether, in those with a diagnosis of ON (which includes ON as CIS), MS-GRS improved prediction of conversion to MS using a Cox model adjusting for known MS risk factors (age of ON diagnosis, sex).

Results:

We identified 2103 individuals with MS, 266 with MS-ON and 421 with non-MS ON by end of cumulative follow-up. The MS-GRS was discriminative of MS (ROC-AUC=0.753). People with non-MS-ON had lower MS-GRS than those with MS-ON (mean 3.02 (SD 1.29) vs 3.71 (1.17), *p*<0.0001), whereas individuals with MS-ON had similar MS-GRS to MS cases without ON (3.62 (1.22) vs 3.71 (1.17), *p*=0.32). In those with an initial presentation ON (n=529, n=121/529 progressing to MS after median (IQR) 21 (12-35) years follow-up), MS-GRS improved prediction of future MS compared to a model using diagnosis age and sex alone, with hazard ratio of 1.31 (95% CI 1.09-1.59, p<0.005) per SD increase in MS-GRS. We were able to stratify individuals into groups of low (4%), medium (23%), or high (43%) future MS risk.

Conclusion:

People with MS-ON have the same MS genetic risk as other MS cases. This novel application of MS-GRS improved risk stratification for future MS diagnosis of ON, including ON as CIS. An MS-GRS integrated into a risk model combined with other demographic characteristics may be found useful for personalising investigation and treatment in individuals with CIS.