Multinational Comparison of the Impact of Polygenic Risk for Multiple Sclerosis on White Matter Integrity in the ABCD Study

Submission ID 3001232

Submission Type Poster Presentation

Topic Brain Structure

Status Submitted

SUBMISSION DETAILS

Please indicate your submission type. Standard Poster

Background Multiple Sclerosis (MS) is an autoimmune disease affecting the brain and spinal cord, impairing nerve signal transmission and leading to a wide range of motor and sensory deficits. MS is moderately associated with genetic and environmental risk factors, making a comprehensive understanding of potential influences crucial to understanding this disease.

Previous work in a Dutch sample reported that adolescents with higher genetic risk of MS, measured via polygenic risk scoring, had detectable differences in measures of white matter integrity quantified using diffusion imaging. Specifically, they found increased global fractional anisotropy (FA) and tract-specific differences in FA and radial diffusivity (RD).

In the current study, we assess the generalizability of these findings to the ancestrally diverse and longitudinally sampled US American population of the Adolescent Brain and Cognitive Development (ABCD) Study (N=9272, ageyr0=9-11, ageyr2=10-14, 4373 F, 4896 M).

Methods MS Polygenic Risk Scores (MS-PRS) were computed using a Bayesian continuous shrinkage polygenic scoring method (PRScs) and independent genome-wide association study summary statistics from the International MS Genetics Consortium. Genetic ancestry in ABCD was estimated using the SNPweights (SNP: single-nucleotide polymorphism) package and external genomic reference panels for African, East Asian, European, and Indigenous American populations.

We identified 33 global and tract-specific imaging phenotypes from ABCD release 5.1 to match those identified in the Dutch study, along with fluid intelligence from the NIH cognition toolbox. Associations between MS-PRS and imaging measures were calculated using generalized linear models controlling for age at scan, sex, scanner software, scanner serial number, and top 10 genetic principal components. Tract-specific analyses also included intracranial volume (ICV) as a covariate. False discovery rate correction was applied to correct for multiple comparisons. Effect size concordance with the original study was assessed using Pearson correlation.

The relationships between MS-PRS and measures of white matter integrity were assessed at baseline and the 2-year follow-up in the European-like genetic ancestry (EUR n=5447) population. We supplemented this analysis with analyses in African-like (AFR n=701) and admixed (MIX

n=3124) genetic ancestry populations. N varied across measure and timepoint.

Results After correcting for multiple comparisons, we were unable to replicate any of the significant findings from the original study in our EUR population at any timepoint. When comparing our effect sizes to those of the original study we found that effect sizes were weakly correlated at baseline (r=0.4, p=0.03) and year-2 follow-up (r=0.4, p=0.03).

There were no significant associations between MS-PGS and any measures in the AFR sample nor was there a significant correlation among the effect sizes.

In the MIX sample, we were able to replicate some but not all of the results of the original study including a positive association between MS-PGS and ICV (p=0.03) and FA in the right cingulate cingulum (p=0.03) and left corticospinal tract (p=0.02). The effect sizes in our MIX sample were also significantly associated with those of the original study at baseline (r=0.7, p<0.01) and year-2 (r=0.4, p=0.01).

Discussion In our primary analysis, we were unable to identify any significant results between MS-PGS and any of our phenotypes of interest in the EUR subsample. The failure to replicate the results of the original study in our analysis has implications for the generalizability of the original findings and may suggest potential differences between European-ancestry adolescents in the Netherlands and those in the US. We were able to replicate some findings from the original study in our MIX subsample, but given the misalignment of ancestry with those used to generate MS-PGS and reduced statistical power, interpretation requires caution and more research.

Please list all co-authors for this poster submission.

* Presenting Author

First Name	Last Name	Affiliation
Jonathan *	Ahern *	University of California, San Diego
Sana	Ali	University of California, San Diego
Abigail	Baim	University of California, San Diego
Sarah E.	Chang	University of California, San Diego
Damion V.	Demeter	University of California, San Diego
Emily M.	Koithan	University of California, San Diego
Sujin	Park	University of California, San Diego
Salma	Zreik	University of California, San Diego
Deanna J.	Greene	University of California, San Diego
Wesley K.	Thompson	Laureate Institute for Brain Research

Chun Chieh	Fan	Laureate Institute for Brain Research
Robert	Loughnan	University of California, San Diego

Keywords

Keywords
Polygenic Risk Score
ABCD Study
Multiple Sclerosis
white matter
diffusion tensor imaging

Congress Attendance & Membership Acknowledgement I Agree.

Signature Jonathan Ahern