MS polygenic risk is not associated with white matter integrity in UK Biobank

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Code: https://github.com/benjacobs123456/PRS_UKB_MRI

Introduction:
Recent studies in healthy children have reported associations between genetic risk of Multiple Sclerosis (MS) and Magnetic Resonance Imaging (MRI) metrics of white matter tract integrity [1,2]. We examined whether MS polygenic risk (MS-PRS) is associated with MRI metrics of white matter integrity in a large cohort of healthy UK Biobank (UKB) participants.

Methods:
We derived and validated an MS-PRS in the non-MRI UK Biobank (UKB) cohort of ~450,000 individuals. Separate scores were derived including and excluding the Major Histocompatibility Complex (MHC) locus. We used imaging-derived phenotypes (IDPs) derived by UK Biobank, encompassing MRI data from ~50,000 individuals [3]. We excluded individuals with Alzheimer's Disease, Parkinson's Disease, and Vascular Dementia. Imaging findings between people with MS and controls was examined in 164 participants with MS and 36,050 controls. Finally, the association between MS-PRS on white matter hyperintensity volume and regional fractional anistoropy was then examined in 32,289 healthy adults using linear regression, adjusting for age, sex, and genetic principal components 1-4.

Results:
Both MHC-containing and non-MHC MS-PRS were strongly associated with MS susceptibility. Individuals with MS demonstrated higher total volume of T2 hyperintensities and near global reduction in regional FA compared to controls. In healthy controls, neither the MHC or non-MHC MS-PRS was associated with T2 hyperintensity volume or regional FA.

Conclusion:
These findings support earlier work [4] suggesting that MS polygenic risk does not correlate with white matter hyperintensity volume or regional FA in healthy adults. Despite the PRS explaining only a small proportion of MS liability, the large sample size here would enable us to detect a small effect of the PRS on MRI phenotypes. Our results therefore argue against the concept that healthy adults with high genetic risk of MS have subclinical MRI evidence of the disease.

References

1. de Mol, C. L., Neuteboom, R. F., Jansen, P. R. & White, T. White matter microstructural differences in children and genetic risk for multiple sclerosis: A population-based study. Mult. Scler. 13524585211034826 (2021).
2. de Mol, C. L. et al. Polygenic Multiple Sclerosis Risk and Population-Based Childhood Brain Imaging. Ann. Neurol. 87, 774–787 (2020).

3. Alfaro-Almagro, F. et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 166, 400–424 (2018).
4. Ikram, M. A. et al. Genetic susceptibility to multiple sclerosis: Brain structure and cognitive function in the general population. Mult. Scler. 23, 1697–1706 (2017).