Validation of a Genome-Wide Polygenic Score for Cognitive Ability in Immune-Mediated Inflammatory Disease

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INTRODUCTION

Individuals with an immune-mediated inflammatory disease (IMID) are at risk of experiencing a lower cognitive ability, in skills such as working memory, attention, and processing speed. There is an association between multiple sclerosis (MS) and reduced cognitive ability, with similar associations in other IMIDs, such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). There is also a strong association of IMID and psychiatric disorders such as anxiety disorders and major depressive disorder, disorders of which have similar detrimental cognitive effects.

Polygenic scores (PGS) of various traits consider polygenicity, the concept of multiple genes influencing a particular phenotype, and various genetic variants associated with a disease or trait, to assess an individual's preponderance for a trait relative to the population. Investigating and validating the IQ PGS within people with an IMID in the Canadian province of Manitoba can give us insight to how this information can be used in clinical settings, specifically when considering care for IMID patients at higher risk for reduced cognitive ability.

AIM

1. Validate the transferability of the IQ PGS in a Manitoban population of individuals by comparing their premorbid IQ scores.

2. Determine whether the IQ PGS differs by IMID disease status (multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis).

METHODS

Participants were recruited in various sites in Manitoba, Canada between July 2014 and June 2016. Individuals were in the following groups: had an IMID (one of multiple sclerosis, rheumatoid arthritis, or inflammatory bowel disease), anxiety or depression, or had neither the IMID nor the anxiety or depression. Sociodemographic and clinical information were captured via self-report questionnaires completed during participants' initial study visit. Interviewers conduced the Structured Clinical Interview for DSM-IV. We used the Wechsler Test of Adult Reading (WTAR), which assesses vocabulary levels with single-word pronunciation tests, as a method to estimate the premorbid IQ of patients within this cohort. Polygenic scores for IQ were calculated for eight different scores based on different p-value thresholds. PGS were calculated for IQ and the GWAS summary statistics were obtained from a published GWAS study for IQ (Savage et al., 2018). We will set the statistical significance level at p≤0.05. All analyses will be performed using R and R-Studio.

RESULTS

Table 1: Sociodemographic and clinical characteristics of the cohort participants.

	Total	MS	IBD	RA	ANX/MDD	Control
N	914 (100)	236 (25.8)	209 (22.9)	148 (16.2)	253 (27.7)	68 (7.4)
Female	691 (75.6)	193 (81.8)	135 (64.6)	125 (84.5)	195 (77.1)	43 (63.2)
Age, y	49.0 (14.6)	51.1 (12.8)	47.6 (15)	59.6 (11.4)	44.5 (12.9)	40.2 (17.4)
Self-reported race						
Caucasian	816 (89.3)	222 (94.1)	197 (94.3)	119 (80.4)	232 (91.7)	46 (67.7)
Non-Caucasian	98 (10.7)	14 (5.9)	12 (5.7)	29 (19.6)	21 (8.3)	22 (32.4)
Lifetime MDD	447 (48.9)	97 (41.1)	87 (41.6)	54 (36.5)	200 (79.1)	N/A
Lifetime ANX	383 (41.9)	74 (31.4)	60 (28.7)	49 (33.1)	209 (82.6)	N/A
Income						
<$50,000	322 (35.2)	75 (31.8)	51 (24.4)	66 (44.6)	110 (43.4)	20 (29.4)
≥$50,000	592 (64.8)	161 (68.2)	158 (75.6)	82 (55.4)	143 (56.5)	48 (70.6)
Declined	25 (10.6)	17 (8.1)	11 (7.4)	8 (7.2)	19 (7.5)	5 (7.4)
Highest education achieved						
High school or below	282 (30.9)	80 (33.9)	63 (30.1)	48 (32.4)	75 (29.6)	16 (23.5)
Above high school	632 (69.2)	156 (66.1)	146 (69.9)	100 (67.6)	178 (70.4)	52 (76.5)
Other	7 (3.0)	7 (3.4)	7 (4.7)	7 (6.3)	14 (5.5)	2 (2.9)
Premorbid cognitive functioning, standard	107.6 (11.3)	106.8 (12.4)	109.1 (9.6)	105.6 (11.9)	108.3 (10.9)	107.9 (11.6)
Premorbid cognitive functioning, raw	38.1 (7.5)	37.8 (8.0)	39 (6.2)	36.6 (7.9)	38.6 (7.1)	38.8 (8.8)

Table 2: Linear regression analyses investigating the association between premorbid cognitive functioning and the IQ polygenic score with and without ancestry outliers removed. the variance in premorbid cognitive functioning (Nagelkerke's pseudo-R2) explained by the IQ PGS as the difference in R2 from the model with the first five ancestry principle components only and a baseline model with the IQ PGS and first five ancestry principle components.

	Minimal adjusted			Full adjusted			Interaction term added to full adjusted model			Full adjusted + adjustment for presence of ANX/MDD			
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Nagelkerke's R^2
Standardized WTAR													
Full cohort	-1.00	0.53	0.06	-1.00	0.53	0.61	-0.15	0.89	0.87	-0.97	0.53	0.07	0.20
Ancestry outliers removed	-0.85	0.57	0.13	-0.83	0.57	0.14	-0.04	0.97	0.97	-0.81	0.57	0.15	0.32
Raw WTAR													
Full cohort	-0.37	0.32	0.24	-0.37	0.32	0.24	0.05	0.59	0.93	-0.45	0.35	0.20	0.07
Ancestry outliers removed	-0.25	0.34	0.46	-0.25	0.34	0.47	0.16	0.63	0.80	-0.31	0.37	0.41	0.02

Table 3: Linear regression analyses investigating the association between the premorbid cognitive functioning and the standardized IQ polygenic score, stratified by disease.

	Minimal adjusted			Full adjusted			Full adjusted + ANX/DEP		
Outcome	Beta	SE	P	Beta	SE	P	Beta	SE	P
Raw WTAR									
MS	-0.15	0.76	0.84	-0.13	0.77	0.87	0.01	0.77	0.99
IBD	-0.35	0.61	0.57	-0.18	0.61	0.77	-0.09	0.61	0.88
RA	0.31	0.94	0.74	0.20	0.94	0.83	0.21	0.94	0.83
ANX/DEP	-1.26	0.63	0.05	-1.28	0.64	0.05	N/A	N/A	N/A
No immune disease nor mental disorder	-0.85	1.76	0.63	-1.47	1.81	0.42	N/A	N/A	N/A

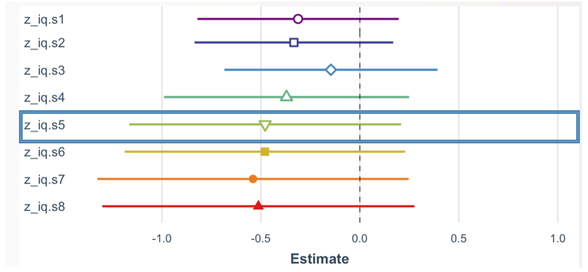

Figure 1: Linear regression investigating the association between premorbid cognitive functioning (**raw score**) and the standardized IQ polygenic score at different p-value thresholds (N=914)

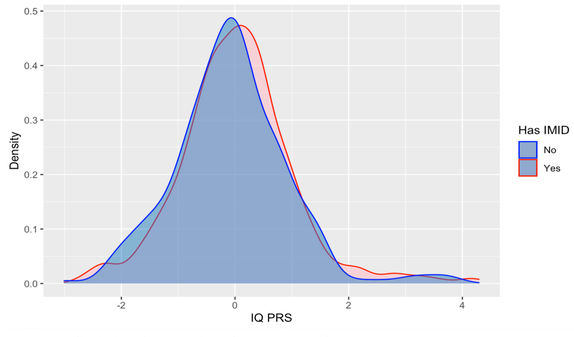

Figure 2. Distributions for the standardized IQ polygenic score comparing the participant population with an IMID and without an IMID. IQ PGS were generated based on a p-value threshold of p≤0.05.

DISCUSSION

The beta estimates across all measurements in this study were predominantly negative. This means that the increase in IQ PGS results in a lower WTAR score. However, no findings were statistically significant (P>0.05) and require further analysis pending genotyping update for the control group.

Limitations: outdated standards for WTAR scores to determine premorbid IQ's, pending genotyping update for the control group.

CONCLUSION

Project was done to provide insight into whether the cumulative genetic burden for IQ are associated with cognitive abilities in a Manitoban cohort. The project is a work in progress -- data should be investigated further.

NEXT STEPS

- Updated genotyping for healthy controls
- Compare other control groups from other public data
- Analyse other cognitive assessments for IQ

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