Reviewer's report

Title: Parkinson disease polygenic risk score is associated with Parkinson disease status and age at onset but not with alpha-synuclein cerebrospinal fluid levels

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Reviewer: Paul Lockhart

Reviewer's report:

The authors present data testing the utility of a polygenic risk score to predict PD risk, age at onset and association with 4 different disease relevant CSF biomarkers (α-synuclein, Aβ1-42, t-tau and p-tau). The study is well described and the rationale and methods are clearly presented. The results suggest that there is a cumulative effect on PD risk and age of onset from known single loci variants (n=16), however there was no significant association with CSF biomarkers. The limitations of the study are acknowledged, the most notable being that a clinically useful PRS remains distant.

Questions and clarifications

1. Please remove the priority claim from Abstract methods regarding GWAs meta-analysis.

2. The 26 PD risk loci account for <10% of phenotype/genetic variability (p4). Given that only 16 of these loci are being captured in the PRS, can the authors comment on the relative phenotype/genetic variability they are assessing?

3. All individuals with known pathogenic mutations (based on the Parkinson Disease Mutation Database) were removed from the analysis (p6). This database annotates α-synuclein, Leucine-rich repeat kinase 2, Parkin, PTEN-induced putative kinase 1 and DJ-1. Has the mutation status of other PD genes been tested in the cohorts and have these cases also been excluded?

4. CSF data was available for a relatively small subset. Were these all derived from one cohort (PPMI or WUSTL) or a combination? Was a similar methodology utilised to determine CSF biomarker levels?

5. It is not clear if the 2 datasets were both genotyped using a mix of all 3 chips or if PPMI was with one platform and WUSTL with another.
6. What was the justification for a call rate >85% as cutoff for inclusion in the PRS? Two loci including AS are very close to this value (0.872), while nearly all of the others are >0.99.

7. It is interesting that dropping the AS variant had minimal effect on the PRS association, given it is by far the most significantly associated variant (independently) with PD status. Have the authors performed any systematic analysis dropping 1 or more variants to investigate the effects on PRS? This might give some preliminary data regarding the number of loci that need to be typed for most cost-effective PRS in the context of PD.

8. Table 1: average values of CSF biomarkers are provided for cases and controls but SD or SEM is given. There is considerable differences in the means of the 2 cohorts for all 4 biomarkers (especially p-tau compared to t-tau). Also please indicate N for each biomarker for the 2 cohorts-the N provided for each cohort (cases and controls) in the table is misleading as there is only biomarker data for 415 cases and 146 controls (methods p6).

9. In Table 2 the MAF is provided for known loci and also this study. Presumably the MAF for known loci is derived from the meta-analysis data (p7 and reference 7). The MAF in this study for several loci (AS, GPNMB, CCDC62 in particular) appear quite different. Are these differences significant? What might be the reason for this and is it likely to affect the results? Notably, an inclusion criteria for this study was population structure (European-American cluster). Were the 16 loci utilised in the PRS all significant in the meta-analysis in the equivalent population? Some clarifying description in the M&M addressing the 16 loci and significance in different populations comprising the meta-analysis would be useful (if the data is available).

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes
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