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: Raffaele Ferrari

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In their article 'Parkinson disease polygenic risk score is associated with Parkinson disease status and age at onset but not with alpha-synuclein cerebrospinal fluid levels' Ibanez and colleagues explored the use of polygenic risk score (PRS) in association with a number of variables including PD risk, age at onset and CSF biomarkers levels in two PD cohorts with available CSF levels for multiple markers such as t/p-tau, AB1-42 and α-synuclein.

It is a shame that authors did not get access to the full summary statistics data, whilst they had full access to the PPMI and (obviously) to the WUSTL data. However, not having access to the full PD summary statistics is clearly not the authors' fault. In the attempt to cope with this issue authors constructed their PRS on the published GWAS hits and were able to make good use of 16/26 of such hits.

Authors were able to establish association with PD risk, age at onset, and, marginally with t-tau CSF levels. Nevertheless, there was no association with α-synuclein levels. These are somewhat interesting results that suggest the importance of tau in neurodegenerative diseases in general and open questions about the genetic architecture of PD and its influence on α-synuclein driven pathology. The latter might be due to power issues as the authors state, nevertheless the PPMI and WUSTL are robust cohorts for studies of this kind.

Authors recognize the limitations of this work in their discussion (i.e. not ideal generating PRS with a partial dataset, but, again this is not their fault); nevertheless, this represents the first step in applying PRS to test the association of PD genetic risk with robust biomarkers datasets. Therefore I would suggest to accept this work for publication to open the way for additional studies of this kind.

A (very) minor point concerns the written English: although the text reads reasonably clearly, in some parts the syntax as well as the wording (i.e. avoiding repetitions in the same sentence) might be attempted to be improved.
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?  
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Yes

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