Reviewer’s report

Title: Targeted next-generation sequencing identifies novel variants in candidate genes for Parkinson’s disease in Black South African and Nigerian patients

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Reviewer: Mathias Toft

Reviewer's report:

The manuscript describes the results of a study sequencing 751 genes in a total of 57 patients with Parkinson's disease (PD). 33 of the patients were Black South African and 14 were Nigerian. The sequencing panel was a neurological research panel and included the most important genes found in familial PD. The authors report that they found more than 14000 rare variants in these patients, including 60 rare variants in 44 genes that were predicted to be deleterious of which 7 rare variants are in three known PD genes.

In most populations, PD is generally a sporadic disease and pathogenic mutations in Mendelian genes are found in 2-5 % of patients. There are very few studies from Africa, so the contributions of known genes are largely unknown. Studies from such populations are warranted.

Despite this there are in my opinion a number of major limitations of the current study:

1. It is unclear to me what the aim of the study actually is. The sample size is very small for a genetic study, and the only thing that can be done is to examine known disease related genes for mutations. However, the patients are not enriched for familial disease or young onset, limiting the chance of finding mutations in known PD genes. There are no families to find new disease genes, no power to do association studies, and no controls to study the frequency of variants found in PD patients in the general population. As a consequence of this, it is very limited which conclusions you can draw based on the presented data.

2. The manuscript is extremely long and detailed, both the abstract and the main text. If the data should be presented as a scientific publication, it needs to be much more stringent in its form.

3. The authors present that the patents had a total of more than 14000 rare variants in the 751 genes, is this more than expected? How to determine which variants that may have a role in disease?
4. On page 13 it is stated that "In order to identify novel PD candidate genes..." How should this be possible given the study design?

5. For the study of rare variants in known PD related genes a less stringent cut off for predicted deleteriousness was chosen. Is there any precedence for this and why was 0.45 selected as a cut-off?

6. Based on the previously mentioned limitations to the study design it makes little sense to perform network analyses based on the results.

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.

No

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

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

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