Author's response to reviews

Title: A Linkage Study of Candidate Loci in Familial Parkinson's Disease

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PDF covering letter
Dear Emma Veitch,

We hereby submit our revised manuscript "A Linkage Study of Candidate Loci in Familial Parkinson’s Disease" by Drs Wirdefeldt, Burgess, Westerberg, Payami and Schalling.

We have revised the manuscript according to the reviewers' suggestions as follows:

Reviewer 1 (Anna Glaser)

Discretionary revisions
1. "In those cases where the selected loci are represented by specific genes it would be possible to sequence the gene in affected and unaffected individuals..."

- We agree with the reviewer that it would be valuable to sequence the genes that have been identified. At present, the only gene that has been sequenced in these families is the α-synuclein gene (Zareparsi et al., Lancet 351, 1998), but we are currently sequencing other known genes. For example, families with an early age of onset are being tested for Parkin. A few of the genes at the loci that we could not exclude from being linked to PD have not yet been identified, but we plan to sequence them as information about them become available.

Compulsory revisions
2. "I would like to see some more of the data from the linkage analysis in individual families..."

- We have added a new table (Table 4) according to the reviewer's suggestion. In this table, we show parametric and non-parametric multipoint lod scores for narrow and broad definition PD for each family and locus in which both parametric and non-parametric lod scores were positive and either of them exceeded the value of 0.5. We have also rewritten the description of the results obtained in individual families ('Results' section; subheading 'Individual pedigree analysis').

3. "I would also like to see some more of the results from the statistical power assessment..."

- We have added a new paragraph with the subheading 'Statistical power calculation' to the 'Methods' section, in which we have developed the description of the statistical power assessment. We now provide detailed information on the assumptions made as well as the results. In short, the estimated mean maximum lod score summarized across all families was 3.75 (standard error 0.046) for narrow
definition PD and 7.48 (standard error 0.055) for broad definition PD. To give an understanding about the estimated lod scores in individual families, we provide the range of values as well as values for the families that gave the lowest and the highest lod score estimates.

Reviewer 2 (Nobutaka Hattori)

1. "The results by the authors are well defined. As the authors performed the linkage studies on only the known loci, the familial Parkinson disease (FPD) could be linked to other loci..."

- We agree with the reviewer that it is possible that PD in these families is linked to loci that were not included in the study. In the 'Conclusions' section, we have added a statement that other loci, known or unknown, may be associated with PD in these families.

2. "The methods are appropriate and well described. However, the authors should consider the autosomal recessive model or affecteds-only model..."

- The majority of families included in the study had a segregation pattern that was consistent with an autosomal dominant mode of inheritance. This is stated in the 'Methods' section, subheading 'Families'. We therefore used this model (autosomal dominant with reduced penetrance) to analyze all loci. The reason why we also used an autosomal recessive inheritance model for the PARK2 (Parkin) locus was that this locus is known to be segregating in an autosomal recessive fashion (Kitada et al, Nature; 392, 1998). Therefore, it seemed plausible to test this locus also under that model. This is explained in the 'Results' section (subheading 'Analysis of narrow definition PD' - 'Parametric linkage analysis', second paragraph). Since the inheritance mode in the majority of the families in the study appeared autosomal dominant, we did not feel it was appropriate to use a recessive model other than for the Parkin locus.

- We agree with the reviewer that an affecteds-only analysis would have been appropriate given the complex phenotype. We carried out this type of analysis for the PARK3 locus since it was initially identified using such an approach (Gasser et al.; Nature Genet, 18, 1998). In the 'Results' section (subheading 'Analysis of narrow definition PD' - 'Parametric linkage analysis', second paragraph), we describe the results of the comparison between the autosomal dominant model with incomplete penetrance and the affecteds-only model. In short, multipoint parametric lod scores increased from between -6.62 and -3.14 for the autosomal dominant model to between -2.98 and -0.73 for the affecteds-only model. In addition, information content dropped significantly. Thus, although affecteds-only analysis would have been preferable, the loss of information content precluded further analyses of this type for the other loci. This is discussed in the second paragraph of the 'Discussion' section.

Sincerely,

Martin Schalling
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Karin Wirdefeldt
MD