Reviewer's report

Title: parkin mutation dosage and the phenomenon of anticipation: a molecular genetic study of familial parkinsonism

Version: 1 Date: 21 January 2005

Reviewer: J William Langston

Reviewer's report:

General

The goal of this study is to determine if anticipation in PD is caused by parkin mutation dosage. To address this question, these investigators analyzed parkin in 19 kindred’s that had early onset disease in the index generation, but late onset disease in the parent generation. There had to be greater than 20 years of anticipation between generations. A group of 28 early-onset patients without anticipation was studied as well. Neurologists at a movement disorder clinic diagnosed all patients. Parkin analysis included sequencing and dosage analysis of all 12 exons. Only one of the 19 cases had a compound mutation, but the affected late-onset parent did not have a parkin mutation, contrary to expectations. On the other hand, 21% of the group without anticipation had mutations. Even though this is essentially a negative result, it addresses an interesting and potentially important question, and contributes new insights in great to this genetic form of parkinsonism.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. It is not clear exactly how a ‘positive family history’ is defined in this study. Was it all first and second degree relatives? Please clarify.
2. It would be of interest to know the breakdown of ages in young-onset patients, both with and without with anticipation, by 5 or at the very least 10 year increments, including some indication which subjects did and did not have mutations; it is recommended that these data be provided.
3. Do the authors have any thoughts on why there appears to be a lower prevalence of park mutations in the families without anticipation (realizing the numbers are very small)?
4. In the first line of the Discussion, the authors indicate that out of 487 patients, 110 demonstrated parkinsonism in successive generations. Where the 487 patients those selected because of a positive family history? If it is a series of all patients seen consecutively in a movement disorders clinic regardless of age, this figure seems extraordinarily high.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions