Author's response to reviews

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

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Version: 2 Date: 21 February 2005

Author's response to reviews:

To: Matt Hodgkinson
Associate Editor, BMC Neurology

Re: MS 4663439905319902 "parkin mutation dosage and the phenomenon of anticipation: a molecular genetic study of familial parkinsonism"

Date: February 18, 2005

On behalf of my co-authors, I wish to thank you for accepting our manuscript for publication.

We made all the formatting changes that were requested.

We realize that we were not required to make the changes that the reviewers suggested. But we found them helpful and made the changes.

In response to reviewer 1 regarding ascertainment bias: We point out the possibility of ascertainment bias both in the Introduction (paragraph 2) and now in Discussion as well. See the last two sentences of paragraph one in Discussion, which we added for more emphasis.

In response to reviewer 2, I would like to address the comments point by point:

1. Positive family history was defined as patient reporting a first or a second-degree relative with PD. Thanks for pointing it out: I inserted the definition in the methods section.

2. As suggested, we now give the ages at onset in increments of 10 years, as well as the range and the mean, for both anticipation and non-anticipation groups. We also specify the ages at onset for mutation carriers. We inserted the following in the text:

page 5: in reference to anticipation families "In the younger generation, 2 probands had onset before age 20, 1 was in his twenties, and 16 were over 30 years old."

page 6: in reference to cases without anticipation "In this group, 3 probands had onset at or before age 20, ε were in their twenties, and 20 were over 30 years old"

page 6: "Nine mutations were found in six individuals. Two subjects were compound heterozygous (onset ages 31 and 37) and four were heterozygous (onset ages 14, 25, 37, 37)."

3. Our thoughts on why there appears to be a lower prevalence of parkin mutations in families with anticipation will have to be off record since numbers are very small. I think there are two issues. One is that anticipation cases are likely different than parkin disease. Two is that parkin may really be recessive. I am not convinced that having a single parkin mutation causes disease.
4. Yes, 487 patients are consecutive; they were ascertained regardless of family history or age at onset. (Although this is a referral clinic, so there is a bias towards familial and early onset). Of the 487 patients, a total of 145 have a first or second degree relative with PD; that is 30% which is in line with the published figures for other referral clinics. What is remarkable is that in 110 of 145 familial cases the affected relative is a parent, aunt or uncle (vertical, dominant looking) and only 35 are siblings and cousins (horizontal, recessive-looking). This gives a perspective on relative frequencies of subtypes within familial PD. I don't think anyone has actually tried to quantify the relative prevalence of vertical vs. horizontal forms within familial PD (I try to avoid using the terms recessive and dominant, because I am not sure all of these cases are in fact genetic).

Thank you for your thoughts, time and help

Haydeh Payami