Author’s response to reviews

Title: Cognition is only minimally impaired in Spinocerebellar Ataxia type 14 (SCA14): a neuropsychological study of ten Norwegian subjects compared to intrafamilial controls and population norm

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Version: 4 Date: 13 November 2013

Author’s response to reviews:

Answers to Referee 2

Comment:
"Title – This is NOT a “case-control” study. You can specify that you had “intrafamilial” as well as population controls."

Reply:
Page 1 in the new manuscript.

The title is changed to "Cognition is only minimally impaired in Spinocerebellar Ataxia type 14 (SCA14): a neuropsychological study of ten Norwegian subjects compared to intrafamilial controls and population norm"

Comment:
The abstract should similarly specify intrafamilial controls or related controls and not just controls.... In the whole section, I am bothered by the use of “controls” and would prefer it to be “unaffected relatives.” Otherwise it might imply unrelated controls or population norms or whatever. At least use the unaffected relative at the beginning of each section.

Reply
Page 3 in the new manuscript

Throughout the manuscript, the term "controls" is changed to "unaffected family members" or "intrafamilial controls". We kept both denominations in order to avoid too much repetitions.
Comment:
In the methods of the abstract it does state intrafamilial, but I do not understand what is meant by “matched.” Perhaps just delete “matched.”

Reply
Page 3 in the new manuscript

The intrafamilial controls are age and education matched, and this is specified in the new manuscript.

Comment:
Although you specify the number of family members, it is difficult to know who they are. I would have preferred comparison of the affected subjects to their unaffected siblings and not to their spouses. It might be good to show the pedigrees or at least to have a column in table 4 that explains who the numbered subjects are. Of course there is assortative mating with respect to intelligence and education level, but the genetic background is different if you are including spouses of the affected offspring and not just the parents. This must be made clear. Perhaps a range of ages of sibs might be helpful.

…In the Methods section of the main body, what does "ten intrafamilial unaffected controls matched for age, education and gender" mean? Average age and education in the two groups? Probably should include an age range for the two groups.

Reply
Figure 1, Table 2 and page 3, 7 and 17 in the new manuscript.

The intrafamilial controls were age and education matched and consisted of six 1st degree and two 2nd degree relatives of the affected, as well as two spouses. Ideally, we would prefer all intrafamilial controls to be genetically related, but the family was too small and no more age and education matched related controls were available. We had to to our best from the family members being available for testing, and even though the spouses don’t share genetic background, their shared socioeconomic background will reduce environmental bias.

We have included a pedigree in the new Figure 1, and added education level and male:female ratios in the new Table 2. In addition, age range for both groups is included in the Methods section.

Comment:
In the conclusion part of the abstract it should be mentioned that the mutation in these two families is not the same as those reported by the other groups. Perhaps there is a genotype/phenotype effect. This could also be mentioned in the Discussion. That is, cognitive impairment is not a common phenotype and may be related to specific mutations.

Reply:
Page 4, 19 and 24 in the new manuscript.

The conclusion part of the abstract is supplemented by: “Genotypic differences may partly account for this discrepancy, and further studies on larger materials are needed to verify the findings.”

In the discussion, we also underline this possible genotype/phenotype effect by stating:

“The differences we find to previous studies could also partly result from genotype specificities, as the mutations reported by other groups were different from the p.H139Q mutation present in our study. Cognitive impairment in SCA14 may thus be associated with specific mutations, rather than being part of a common phenotype. As few families with SCA14 have so far been reported, genotype/phenotype correlations are, however, not yet investigated.”

In the Conclusion we state that:
“Genotype-phenotype correlations remain to be studied for cognition in SCA14.”

Comment:
In Results, rather than “The mutation was not found in intrafamilial controls,” I’d suggest stating that intrafamilial controls were relatives who did not carry the mutation.

Reply:
Page 7 in the new manuscript.

The sentence “The mutation was not found in intrafamilial controls” is deleted, and it is stated in the Methods section that "Ten family members, six females and four males, were included as intrafamilial controls. None of them carried the SCA14 mutation.”

Comment:
I’d suggest referring to Table 4 earlier (change it to Table 1). Otherwise it is very difficult to follow all the psychologic testing results. And as mentioned, having pedigree numbers without knowing who are the parents of which sibship is not sufficient.
Reply:

As Table 1 is referred to already in the Background section, we choose to refer to the old Table 4 as Table 2, together with the new Figure 1, which shows the modified pedigree of Family 1. In order to make the subjects less identifiable, we do not specify which subjects in Table 2 that correspond to specific subjects in Figure 1.

Comment:

In the Discussion, I do not understand the use of the word “phenocopy” in the section on bias. I don’t find that sentence helpful at all.

Reply:

Page 17 in the new manuscript.

A phenocopy is a phenotypic trait or condition that is induced by environmental factors but closely resembles a phenotype usually produced by a specific genotype. In our study we cannot exclude that environmental factors, as living with the affected and being exposed to the same social environment, may have had an impact on the cognitive profile of the unaffected family members. We expand the explanation of this with "In addition, the unaffected family members may be influenced by the affected, inducing a certain amount of phenocopy effect."