Author’s response to reviews

Title: Cognition is only minimally impaired in Spinocerebellar Ataxia type 14 (SCA14): a neuropsychological case-control study of ten Norwegian subjects

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Author’s response to reviews: see over
We thank the reviewers for a very thorough and relevant review and are pleased to submit the revised version of the study "Cognition is only minimally impaired in SCA14; a neuropsychological case-control study of ten Norwegian subjects".

The manuscript has been reviewed according to the three reviewers’ comments and suggestions.

The main point was the introduction of a matched control group. We were aware of the need for matched controls, and when the study was designed an intrafamilial control group was included and tested. In order to present our findings in a more concise way, we chose to leave out the results from this control group when writing the manuscript, after much hesitation. We are therefore very happy to be able to present our results as compared to controls on the request of the reviewers. We agree that the comparison to unaffected family members with the same genetic and environmental background gives a more precise answer to the main question in this study – in what way PRKCG mutations may affect cognition. The inclusion of the intrafamilial control subjects changes the results section and of course the discussion. This also means that rather important changes had to be done in the article (results and discussion) to make place for the controls. We have bolded and highlighted in yellow the added text, while other changes done in the text after the reviewers’ comments are merely highlighted in yellow.

We are very grateful for the constructive reports from the external reviewers and hope their questions are better answered in the revised manuscript. Regarding the tables, the biggest changes are done in Table 2, where we have added four new columns. We have tried to present as extensive and informative results as possible in this table, at the risk of making the table too heavy. We will be pleased to modify this table if it is considered more appropriate.

As reviewer 1 noted, no longitudinal data on cognition in SCA14 exists. We are planning on retesting the patients within three years in order to establish follow-up data on both motor and cognitive progress in this rare disorder.

**Answers to Referees commenting the SCA14 manuscript:**

**Referee 1**

**Comment:**
"One weakness of this study is the lack of a matched control group especially with the same linguistic background (mother tongue). The authors used published control cohorts for comparison but social background and mother tongue may influence test performance and especially rapid generation of words starting with specific letters as one of the tasks with major deficits in the SCA14 cohort"

**Reply:**
Table 2
Page 6, 7 and 17 in the new manuscript.

We were aware of the need for matched controls, and when the study was designed an intrafamilial control group was included and tested. In order to present our findings in a more
concise way, we chose to leave out the results from this control group when writing the manuscript, after much hesitation. We are therefore very happy to be able to present our results as compared to controls on the request of the reviewer. The intrafamilial controls shared linguistic and social background with the affected subjects, and as pointed out by the reviewer, the rapid generation of words starting with specific letters was indeed different in controls and norm, possibly due to mother tongue differences.

Comment:
“Within the SCA14 group the authors included one individual who claimed to carry the mutations but was clinically asymptomatic. If included in this study at all, genetic test results must be confirmed since this individual is almost 10 years older than the latest age of onset in the other patients. Anyway, her results should be presented separately and should not be merged with patients with manifest disease to prevent bias”

Reply:
Table 2 in the new manuscript.
Page 7, 16 and 22 in the new manuscript.

This subject is confirmed to have the mutation, but has no motor symptoms and signs from the disease. In order to answer our main question – whether SCA14 mutations affect cognition, we found it appropriate to include this subject. Nevertheless, this was not an evident choice, and we have now excluded the subject from the group analyses and presented the individual scores in a separate column in table 2. It is of interest, however, to see that this subject shows the scores in the lower range of the affected subjects with better non-verbal than verbal functions. The overall group results did not change when this subject was excluded from the analyses.

Comment:
“In this cross-sectional neuropsychological study the authors did not observe accentuation of cognitive deficits with duration of disease. On the contrary, they speculate that the tendency to better test performance with longer disease duration reflects compensatory brain plasticity that helps to improve cognitive function with time. This is highly speculative and neither a significant result nor supported by longitudinal data. Such speculation should be omitted at least from the abstract and conclusions.”

Reply:
Page 16, 21 and 22 in the new manuscript.

We do agree that the positive correlation between IQ and duration of disease is weakly supported statistically, and may be coincidental in this small cohort. The secondary aim of our study was to assess the relationship between duration and motor severity of the disease to the neuropsychological performance. The relationship between IQ (and WCST performance) to disease duration was the most convincing correlation results we found, and as it did not support our hypothesis of aggregation of cognitive impairment with duration, we believe it is right to report these finding. However, following the reviewer’s comment, we have been careful to mention our hypothesis concerning a relation with brain plasticity only in the results and discussion section. Regarding longitudinal data, we intend to establish this by by retesting the patients within three years.
Referee 2

Major Compulsory Revisions

1. Comment:
“Unfortunately, a major limitation of the work was not even mentioned: the absence of comparison data from unaffected biologic relatives. Both genetic and environmental factors contribute to performance on the tasks used in this study and the affected and unaffected members of the families share these contributors. You cannot just assume that these families would have exactly population-average performance on all the tests. In fact, the authors acknowledge that the families are from industrial areas and may lack in academic experience. Therefore, the conclusions are difficult to assess.”

Reply:
Table 2 in the new manuscript.
Page 6, 7 and 17 in the new manuscript.

We were aware of the need for matched controls, and when the study was designed an intrafamilial control group was included and tested. In order to present our findings in a more concise way, we chose to leave out the results from this control group when writing the manuscript, after much hesitation. We are therefore very happy to be able to present our results as compared to controls on the request of the reviewers. We agree that the comparison to unaffected family members with the same genetic and environmental background gives a more precise answer to the main question in this study – in what way the PRKCG mutation affect cognition. We still think it is of value to also report the results compared to population-average performance, as this gives insight to the cognitive profile of the patients as compared to the background population, even though we primarily focus on the differences to controls.

2. Comment:
“Similarly, the title may be wrong. What if the unaffected people in the family have superior performance on the tests? Then the impairment related to SCA14 may be more than minimal.”

Reply:
Table 2
Page 17, 18, 20, 21 and 23 in the new manuscript

After the inclusion of controls from the family, the title is even better supported. As we see only minimal impairment and even some superior performances to controls, we believe “Cognition is only minimally impaired in Spinocerebellar Ataxia type 14” is a valid title for this study.

Discretionary Revisions

1.
Comment:
“When cognitive test results for the affected family members are available, a related, but less important, comparison of interest would be to analyze the families independently. This might provide insight on whether there is a similar cognitive phenotype in the two families that share the same PRKCG mutation on different genetic and environmental backgrounds”.

Reply:
Table 2
Page 22 in the new manuscript

The question of whether there is a similar cognitive phenotype in two different families with the same mutation is very interesting. Unfortunately, only one member from the second SCA14 family lives in Norway and is available for testing. We have now included the individual results from this subject in table 2. He is still also included in the group analyses in the same table. Interestingly, this subject shows the same cognitive pattern characterized by impaired verbal executive functions and intact non-verbal executive functions as the subjects from family 1.

2. 
Comment
“With respect to the relationship of IQ to duration of disease, the number of subjects is so small that, without a better comparison group, “trends” seem meaningless to me.”

Reply:
Page 16, 21 and 22 in the new manuscript.

We do agree that the positive correlation between IQ to duration of disease is weakly supported statistically, and may be coincidental in this small cohort. The secondary aim of our study was defined to assess the relationship between duration and motor severity of the disease to the neuropsychological performance. The relationship between IQ (and WCST performance) to disease duration was the most convincing correlation results we found, and as it did not support our hypothesis of aggregation of cognitive impairment with duration, we believe it is right to report this finding. However, we have now underscored the speculative nature of this hypothesis and avoided the use of the concept “trend”.

Referee 3

Minor Essential Revisions
Comment:
“Authors described that the trends towards higher IQ at longer disease duration and more disease severity. I am confused for this result. Please explain it well.”

Reply:
Page 16, 21 and 22 in the new manuscript

Duration of disease showed a correlation to higher IQ, although not to the level of significance ($r=0.61, p=0.081$), which implies that the subjects with the longest duration of symptoms had the highest score on IQ. We observed that the subject with the longest duration (27 years) also had the highest total IQ performance (IQ=107). We are aware that this finding
may be coincidental in this small study, and it is poorly supported statistically. Nevertheless, it was defined as a secondary aim of our study to assess the relationship between duration and motor severity of the disease to the neuropsychological performance. The relationship between IQ (and WCST performance) to disease duration was the most convincing correlation results we found, and we believe it is right to report this finding, especially as it did not support our hypothesis of aggravation of cognitive symptoms with disease duration. However, we have in the revised manuscript underscored the speculative nature of this hypothesis.