Reviewer’s report

Title: High frequency of Machado-Joseph disease identified in Southeastern Chinese kindreds with spinocerebellar ataxia

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Reviewer: Conceição Bettencourt

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The authors present a work in which they have analyzed the Machado-Joseph disease (MJD) locus in a sample of 150 healthy Chinese individuals and in 138 probands of autosomal dominant SCA families from several regions of Southeastern China. From the analysis of the distribution of the ATXN3 wild-type alleles in normal individuals, the authors report a positive skew and high frequencies of large normal alleles. On what concerns the SCA patients, a CAG expansion at the ATXN3 gene (>60 repeats), the causative mutation of MJD, was observed in 100 of the total 138 probands, leading to the highest MJD frequency (72.46%) reported so far for Asian countries. The authors attribute this high representation of MJD, in the analyzed population, to a high frequency of ATXN3 large normal alleles, from which the expanded ones could be emerging. Furthermore, the authors used La Taq DNA polymerase, which seems to improve the amplification of expanded alleles and thus contribute to the increased number of molecularly confirmed MJD cases. The data presented here contributes to the knowledge of the epidemiological representation of MJD, and constitutes a basis for comparisons in forthcoming studies. Furthermore, the usage of La Taq DNA polymerase was shown to improve the molecular diagnosis of MJD.

Major Compulsory Revisions

1. Although reading the paper we can infer the questions pointed by the authors, the work hypothesis should be clearly stated in the Abstract and in the Background sections.

2. In the Methods section, the authors should specify the number of the sequenced samples. Furthermore, statistical analysis should be further detailed.

3. The results of the present study raise the hypothesis that the large normal alleles may constitute a reservoir from which the expanded allele may be emerging and the authors affirmed that “the high frequency of MJD may be attributed to the high frequency of large ANs in the present study”. Is there any evidence of de novo mutations that could support this statement?

4. The results from the comparison between LA Taq and Taq polymerase are only mentioned in the Discussion section. They should come first in the Results section and the corresponding methodological aspects should be explained in Methods. Were the PCR reaction conditions the same? How many samples were
used in the comparison? What was the estimated error for amplifications with Taq polymerase?

5. In the Discussion section, the authors wrote: “we suppose that Asian origin of MJD and founder effect may also contribute to the high frequency of MJD in the present study”. Could the frequency of the large normal alleles be also affected by a founder effect? What other factors could be influencing the distribution of wild-type alleles?

Minor Essential Revisions

6. In the Background section, the authors state “The characteristics of CAG repeats in a large normal population including Acadian, African American, Caucasian, Greenland Inuit and Thai individuals were analyzed in 1996 [14]”. Without disregarding the importance of the referenced work, there are several and more recent studies in this field, why the restriction to this reference from 1996?

7. In the end of the “Analysis of CAG repeats in normal individuals” from the Results section, the authors wrote: “In accordance with the previous report, … (>27 repeats) were defined as large ANs [21]. The frequencies of large ANs in the present study were calculated and compared to those of Japanese … and Thai [14].” In those two sentences, the authors are explaining methodological aspects, thus they should come in the Methods section, and in the Results the authors should only refer to table 1.

8. In the Results section, where it is “estimated to contain 14 CAG repeats is confirmed by sequencing” it should be “estimated to contain 14 CAG repeats was confirmed by sequencing”

9. In the Discussion section, where it is “which was also the most common allele found in the study of Limprasert et al [14] and Takano et al [21].” It should be “which was also the most common allele found in the studies of Limprasert et al [14] and Takano et al [21].”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests