LETTER TO THE EDITOR

Reply: Replicating studies of genetic modifiers in spinocerebellar ataxia type 3: can homogeneous cohorts aid?

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Sir,

Thank you for the opportunity to reply to the correspondence concerning our recent publication in Brain, ‘Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes’ (Tezenas du Montcel et al., 2014). We read with great interest the letter and we thank the authors for their insights.

To replicate findings is essential. As we mentioned in the discussion, replication studies can be limited by several pitfalls. The size of the replication cohorts is often limited and thus the power of the replication studies is often limited. Also, differences in CAG repeat size or phenotypic expression in affected subjects of different ethnic or geographic origins (Subramony et al., 2002) might explain why these

Figure 1 Summary of interactions among (CAG)n-containing genes in the EUROSCA cohort. For the SCA type, the black labels indicate the gene, the blue label, the age at onset of individuals with an expansion of the gene. Black arrows are for marginal effect whether green arrows are for effect in interaction with the major gene. Nb > 12: = alleles with more than 12 repeats; Interm = intermediate allele; + = positive effect; − = negative effect; Shorter = shorter allele; Longer = longer allele; Longer > 25 = longer allele with > 25 repeats; Difference = difference between the longer and the shorter allele.
results were not found in our large SCA series. This is particularly the case for genetic studies where genetic factors can be due to founder effects such as the Azorean population for SCA3 or the Cuban population for SCA2. This can also be due to differences in clinical characteristics of the patients, in particular due to sampling differences: hospital versus population-based samples for instance. This highlights the importance of describing the studied population with care.

Raposo et al. replicated in the Azorean population our finding of a quadratic effect of the ATXN3 expanded allele in SCA3 patients, strengthening our finding. They failed to replicate the effect of the ATXN2 and ATN1 genes found in the EUROSCA population only and were not able to test for the effect of the HTT gene.

In addition, Raposo et al. report the negative correlation at the longer allele at the ATXN1 gene with the age at onset of the SCA3 patients. As this finding was not significant in the EUROSCA study, we did not test it in the replication cohorts. We have now tested this effect in our replication cohorts and found a significant effect in the FRA cohort ($R^2 = 0.623, P = 0.011$) and failed to find an effect in the CRC cohort. We can thus propose a modification of the summary figure proposed in the Tezenas du Montcel et al. (2014) publication (Fig. 1).

References
