Mitochondrial Complex I Gene Variant Associated With Early Age at Onset in Spinocerebellar Ataxia Type 2

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Background: A common mitochondrial complex I gene polymorphism (10398G) is reported to be inversely associated with the risk of Parkinson disease. We hypothesized that this variant might have a protective effect on the central nervous system and therefore might delay the onset of symptoms in spinocerebellar ataxia type 2 (SCA2).

Objective: To assess the association of the 10398G polymorphism with age at onset in Cuban patients with SCA2.

Design: Genetic association study.

Setting: Holguin, Cuba.

Patients: Forty-six Cuban patients with SCA2.

Main Outcome Measures: Presence or absence of the 10398G polymorphism was determined in 46 Cuban patients with SCA2 and early or late onset of symptoms, defined as at least 2 SDs lower than or higher than the mean age at onset for patients with a similarly sized triplet repeat expansion.

Results: The polymorphism was present in 11 of 27 Cuban patients with SCA2 and early onset (41%) vs 2 of 19 with late onset (11%) (Fisher exact test; P = .04).

Conclusion: Contrary to our prediction of a later onset of SCA2 in patients with the 10398G polymorphism, we find that this variant is associated with an earlier age at onset in Cuban patients with SCA2.

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Spinocerebellar ataxia type 2 (SCA2) is caused by a triplet repeat expansion in the ataxin-2 gene. The age at onset is loosely correlated with the size of the triplet repeat expansion, a feature common to several triplet repeat disorders. However, there remains considerable variability in the age at onset for any given triplet repeat length, indicating that other genetic and/or environmental factors influence the age at onset. In Cuban patients with SCA2, CAG repeat length has been determined to account for 57% of age at onset variance, with normal variations in the CAG repeat length in the CACNA1A calcium channel subunit gene accounting for 5.8% of the remaining variance in age at onset in this population. The additional factors that account for the remaining variance in age at onset are unknown.

Mitochondrial dysfunction plays a role in the pathogenesis of Friedreich ataxia and also in other triplet repeat disorders. We therefore hypothesized that mitochondrial DNA variants might influence the age at onset of SCA2. The 10398G polymorphism was selected for analysis based on its reported association with a lower risk of Parkinson disease, with the prediction that it might be associated with later onset of symptoms in SCA2. Surprisingly, we find instead that this variant is associated with early onset of symptoms.

Methods

Patients with SCA2 from the Holguin province in Cuba were identified and recruited as previously described. The age at onset and SCA2 CAG repeat length were determined in 394 patients with SCA2. The DNA was available for 46 patients from this group with ages at onset that were 2 SDs lower than or higher than the mean age at onset after adjustment for SCA2 repeat length. In addition, these patients were known not to share a common maternal grandmother. The presence of the 10398G polymorphism was determined in 46 Cuban patients with SCA2. The DNA was available for 46 patients from this group with ages at onset that were 2 SDs lower than or higher than the mean age at onset after adjustment for SCA2 repeat length. In addition, these patients were known not to share a common maternal grandmother. The presence of the 10398G polymorphism was determined by polymerase chain reaction amplification of blood-derived DNA followed by restriction endonuclease analysis, as previously described. A Fisher exact test was used to compare the frequency of the 10398G polymorphism in patients with early vs late ages at onset.
RESULTS

The mean ± SD number of CAG repeats among early-onset cases was 39.6 ± 2.4, with a range of 36 to 43. Among late-onset cases, the mean ± SD number of CAG repeats was 40.3 ± 3.9, with a range of 36 to 52. The mean age at onset among the early-onset cases was 22.9 ± 8.6 years, with a range of 11 to 43. For late-onset cases, the mean age at onset was 42.4 ± 12.9 years, with a range of 23 to 64. The 10398G ND3 variant was present in 11 of 27 early-onset SCA2 cases (41%). In contrast, this variant was present in only 2 of 19 late-onset SCA2 cases (11%). The variant was homoplasmic in every case (see Figure and Table).

COMMENT

Like other triplet repeat disorders, SCA2 is associated with an inverse association between the length of the triplet repeat expansion and the age at onset of the disease. However, CAG repeat length accounts for only 46% of the variance in age at onset in SCA2 and approximately 57% of the variance in the Cuban SCA2 population. Relatively little is known about the factors that account for the residual variance in the age at onset. Although the CAG repeat length in the CACNA1A calcium channel subunit gene accounts for a small fraction of the remaining variance, the additional factors that influence the age at onset in SCA2 are unknown.

The Cuban SCA2 founder population in the province of Holguin provides a population with a relatively homogeneous genetic background and many shared environmental factors. This may facilitate the ability to detect genetic factors influencing age at onset, although a disadvantage is the uncertainty regarding the applicability of results from this specific population to other populations. To further increase the chances of detecting an influence of a genetic factor on the age at onset, we limited the analysis to Cuban patients with SCA2 and unusually early or unusually late ages at onset after accounting for the number of CAG repeats.

Mitochondrial dysfunction is a feature common to several polyglutamine disorders and to Friedreich ataxia, raising the possibility that genetic factors that affect mitochondrial function might influence the age at onset of SCA2. We chose to analyze a common variant in a mitochondrial complex I gene, the 10398G polymorphism, based on the reported association of this mitochondrial complex I gene variant with a reduced risk of Parkinson disease. We hypothesized that this variant might confer a protective effect in the central nervous system that could lead to a later onset of symptoms in SCA2. We did not confirm this hypothesis. In contrast, the 10398G polymorphism was associated with an earlier age at onset in SCA2.

It is unlikely that the lack of detection of a protective effect was due to lack of power, since we chose patients with SCA2 who were highly discordant for age at onset after correction for the effect of the SCA2 repeat length. It is possible that the effect of the 10398G variant differs in Parkinson disease compared with SCA2 or is influenced by the particular genetic background and environmental factors seen in this Cuban population. In addition, population differences may explain the divergent results. The inverse association of this variant with the risk of Parkinson disease reported by van der Walt et al was also seen in Spanish subjects. However, this inverse association was not found in an Italian population, and a prior study in the United States failed to find this association after controlling for ethnicity. It is also possible that the 10398G variant is a marker for another mitochondrial DNA variant that influences the age at onset of SCA2. The limited numbers of subjects available for this study precluded similar analyses of less common mitochondrial variants. In any case, the data presented do not support the hypothesis of a central nervous system–protective effect of the 10398G variant in Cuban patients with SCA2 and instead suggest an association of this variant with early onset of symptoms. Future studies are needed to assess the association of this mitochondrial DNA variant with age at onset in other SCA2 populations and to test for a similar association in other triplet repeat disorders.
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REFERENCES