Frequency of CAG-Triplet Repeat Expansions in Three ATXN Loci in Patients with Spinocerebellar Ataxia (SCA)

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Abstract

Autosomal dominant spinocerebellar ataxias (SCAs) are a complex group of neurodegenerative disorders. The diseases affect the cerebellum and its main connections causing a generalized incoordination of gait, speech, and limb movements. There are at least 31 subtypes of spinocerebellar ataxias. The causative genes have been partly characterized and the frequency of each gene mutation varies among ethnics. Genetic testing is needed to determine the certain type of SCA in an affected person due to an overlap of symptoms among the different types of SCAs. The most three commonest subtypes found worldwide are SCA1, SCA2 and SCA3 (Machado-Joseph disease, MJD) of which the defect caused by an expanded-CAG repeat in coding sequence of the particular genes, including ATXN1, ATXN2 and ATXN3, respectively. We studied here the frequencies of the three SCA subtypes from 480 unrelated SCA patients subjected to genetic testing at our laboratory (2001-2013) including 232 (48.33%) men and 248 (51.67%) women. CAG-repeat expansion analysis was performed by initially isotopic-PCR followed by polyacrylamide gel electrophoresis and finally fluorescence-PCR together with capillary electrophoresis. The positive cases of SCA due to the presence of CAG-repeat expansions were found in 146 (30.42%) patients. Subtyping by molecular results revealed that SCA3 was found in 16.5% (79/480), SCA1 38 (8.04%) and SCA2 in 6.05% (29/480) of all patients. The number of expanded CAG repeats varies from 42-54 repeats (common allele = 45 and 46 repeats, 18% for each) in SCA1 and 35-54 repeats (common allele = 41 and 42 repeats, 14% for each) in SCA2. Interestingly, one patient was found to carry the intermediate/borderline size of ATXN3-CAG repeats (42 repeats) with no ATXN1 and ATXN2 mutations. The CAG-repeat expansion in ATXN3 was the most common cause of SCA in Thailand, while those in ATXN1 and ATXN2 should be ordered as the second one with similar frequency. These frequencies are concordant with the previous report in Thailand (Sura T. et al., 2009). The identification of the causative CAG expansion enables the molecular diagnosis of the different SCA subtypes and facilitates genetic counseling for family planning of the patients. Mutation-negative patients (333 patients, 69.4%) from this study may be of other SCA subtypes i.e. SCA6, SCA7, SCA17 and dentatorubral-pallidoluysian atrophy (DRPLA) which are still remained for investigation of CAG expansion in other genes. Furthermore, these patients may be affected by neurological disorders with ataxia with unknown etiological factors.

Keywords: spinocerebellar ataxia, SCA, CAG-repeat expansion

References

1. Sura T, Manop P, Kanjanawong P, Limwongse C. Frequency of CAG triplet repeat expansions in three ATXN loci in patients with spinocerebellar ataxia (SCA) in Thailand. National Genetics Conference 2013 (NGC2013) including 232 (48.33%) men and 248 (51.67%) women. CAG-repeat expansion analysis was performed by initially isotopic-PCR followed by polyacrylamide gel electrophoresis and finally fluorescence-PCR together with capillary electrophoresis. The positive cases of SCA due to the presence of CAG-repeat expansions were found in 146 (30.42%) patients. Subtyping by molecular results revealed that SCA3 was found in 16.5% (79/480), SCA1 38 (8.04%) and SCA2 in 6.05% (29/480) of all patients. The number of expanded CAG repeats varies from 42-54 repeats (common allele = 45 and 46 repeats, 18% for each) in SCA1 and 35-54 repeats (common allele = 41 and 42 repeats, 14% for each) in SCA2. Interestingly, one patient was found to carry the intermediate/borderline size of ATXN3-CAG repeats (42 repeats) with no ATXN1 and ATXN2 mutations. The CAG-repeat expansion in ATXN3 was the most common cause of SCA in Thailand, while those in ATXN1 and ATXN2 should be ordered as the second one with similar frequency. These frequencies are concordant with the previous report in Thailand (Sura T. et al., 2009). The identification of the causative CAG expansion enables the molecular diagnosis of the different SCA subtypes and facilitates genetic counseling for family planning of the patients. Mutation-negative patients (333 patients, 69.4%) from this study may be of other SCA subtypes i.e. SCA6, SCA7, SCA17 and dentatorubral-pallidoluysian atrophy (DRPLA) which are still remained for investigation of CAG expansion in other genes. Furthermore, these patients may be affected by neurological disorders with ataxia with unknown etiological factors.