Letter to the Editor

Large normal alleles and SCA2 prevalence: lessons from a nationwide study and analysis of the literature

To the Editor:

The relationship between high frequency of large normal alleles (LNA) and high prevalence of autosomal dominant cerebellar ataxias (ADCA) is not completely understood. Inconsistent reports regarding this relationship have been published, some of them postulating strong correlation between LNA and expanded alleles (EA) of the dominant spinocerebellar ataxias (SCAs) (1). Here, we provide epidemiological and genetic data supporting the hypothesis of large normal alleles (LNA) being a reservoir of EA in SCA2(ATXN2). We also discuss the reasons of conflicting data in the literature.

We developed nationwide genetic ataxia screening (2), and was found that the highest prevalence of SCA2 worldwide relates to the highest frequency of 23–31CAG repeats in Cuban population (Fig. 1a,b). Pre-mutated alleles in SCA2 families displayed meiotic and mitotic instability (3). Analysis of the epidemiological data revealed a linear correlation ($r^2 = 0.8408$, $p < 0.000$) between LNA-SCA2 frequencies (Fig. 1c). We also present a family with a progressive CAG elongation (from 31-to-33CAG), linked to the ancestral C-C-SNP-haplotype (Fig. 1d), supporting the original postulate (1).

The hypothesis outlined by Takano et al. (1) was assessed in 11 populations. In summary, the LNA–EA relationship has been confirmed in the majority of populations and only one study involved a nationwide screening (Table 1). Therefore, inconsistencies between

![Fig. 1](image_url)

**Fig. 1.** (a) CAG repeats size distribution at the SCA2 locus in the Cuban population. The distribution is shifted toward ANs according to our previous data (3). (b) Comparison of large ANs frequency of in Cuban vs other populations. (c) Correlation between large normal (LN) frequency and relative SCA2 frequencies in different populations. LN and SCA2 frequencies were collected from reports in Table 1. (d) Genealogy and genotype of the SCA2 family showing expansion from a LN to abnormal SCA2 repeat expansion. SNP haplotypes and CAG repeat sizes were revealed by sequencing using FP3-RP3 primers. Intragenic SNPs rs695871 (G/C) and rs695872 (T/C) are situated at positions 106 and 177 nucleotides upstream of the CAG repeat. CAG for other cases were obtained by fragment analysis as reported in (3).
studies could be the consequence of restricted representation of normal/pathological CAG-repeat spectrum. Collection of control samples is simpler than obtaining samples from ataxics and differential distribution may result from selection bias related to unequal access to specialized medical services.

Polish and Finnish studies provided discrepant results. Poland had high prevalence of LNA while SCA2 being recently found as the second most common SCA subtype (9, 12), supporting the correlation of LNA-SCA2 prevalence.

Finnish population have different occurrence of genetic diseases (10), explaining the lack of controls and ATXN2-pathological alleles relationship. No excess of LNA in Indian controls compared with Finns was observed, but would not be conclusive. Note, that nine Indian populations were not enriched with LNA as only in Brahmin and Mahishya ethnicities, >27 CAG has been found. India is a multiethnic (>200) country of ‘one billion people’, and genetic diseases are clustered in ethnicities. Phenotypically similar families to SCA2 have been reported but without genetic localization, thus it is not clear whether SCA2 is the most frequent SCA in India, unless nationwide screening is undertaken (6, 13).

The clinical spectrum of SCA2 is the broadest among all SCAs, and may present as cerebellar, parkinsonism, motoneuron, psychiatric phenotypes or infantile encephalopathy with genetic overlap. Moreover, differences in age-of-onset and non-Mendelian inheritance represent serious diagnostic challenges for clinicians. These cases are often gathered not for the CAG expansion, modifying the real picture regarding mutation incidence. Penetrance is uncertain between 32-35CAG-repeats. The carriers of such expansions usually have a very late disease onset resulting in limited accessibility, correct clinical assessment and hence classification within the SCA subtypes. There are inconsistencies in the consensus thresholds for LNA/intermediate and pathological CAG expansions. In fragment analysis, the (CCG/CCG)n polymorphic sequence repeats adjacent to CAG is counted as part of the repeat expansion. All the above-mentioned issues contribute to discrepancies between predisposed alleles and the disease incidence, in SCA2 as well as in other SCAs.

What should be therefore kept in mind? In the populations with highest SCA2 incidence, the highest LNA frequency is found. De novo pathogenic CAG expansions are more likely to occur from LNA. Their presence represents an increased intergenerational risk (>0%) for disease development which should be communicated with the carriers. Wide clinical expressivity, penetrance, pleiotropism of ATXN2 mutation, and technical errors contribute to ‘discordant results’ concerning the hypothesis on LNA being reservoirs for EA in SCA2 and conditions connected with ATXN2-CAG expansions.

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J. M. Lafitta-Mesa,a,b,*
L. E. Almaguer-Mederos,a,b
V. Kourň
P. O. Bauer
Y. Vázquez-Mojena
T. Cruz Mariño
L. Velázquez-Pérez,a,b

aCenter for Research and Rehabilitation of Hereditary Ataxias – CIRAH, Holguín, Cuba
bBranch of Biomedicine of the Cuban Academy of Sciences – ACC, Havana, Cuba
Virology Department, Institute of Tropical Medicine “Pedro Kourň”, Havana, Cuba, and
Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA
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References


Correspondence:
José Miguel Laffita-Mesa, PhD
Calixto García 152b
Antilla, Holguín
Cuba
Tel.: +53 24 461564
Fax: +53 24 463579
e-mail: laffita@ataxia.hlg.sld.cu