THE CONTRIBUTION OF THE SELF POLYQ LOAD [SOMATIC MOSAICISM] IN THE CNS TO THE ONSET, DISEASE DURATION AND PROGRESSION RATE OF SCA2

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Introduction: SCA2 show strong relationship among CAG and the onset of ataxia. Other factors might accounts for the onset and other phenotypic features. The best modifier might be intrinsically depending/causing of the unstable nature of the CAG.

Aims:

1) To compare the somatic mosaicism of the expanded CAG of SCA2 gene in CNS.

2) To determine the influence of somatic mosaicism on SCA2 phenotype and its relationship with CAG size and architecture and haplotype.

3) To gain insights about the dynamic of the CAG expansion in CNS of SCA2.

Methods: We have analyzed CAG expansions in 12 different sites of SCA2 deceased patients with discordant phenotypes and somatic mosaicism indices, peaks number, CAG range and skewness of the CAG in each region were determined. Also, detailed clinical data using rating scales trough life with follow-up using neurophysiology biomarkers were used to generate phenotypic profiles.

Results: Regions of the brain with greatest level of somatic mosaicism were motor cortex, occipital grey matter, olive, pons, and globus pallidus. While those regions more compromised in SCA2, like cerebellar cortex showed lesser somatic mosaicism. Early onset was associated with wide ranges of CAG in the CNS (with differences up to 10-17 CAG units respecting the major CAG) in contrast to delayed onsets. Sequence and STR haplotype altogether with phenotypic data are also presented.

Conclusions: Our results bring data about the role of the somatic mosaicism as the major modifier of the SCA2 phenotype.