DNA repair genes *and ATXN2* change the age at onset of MJD

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**ABSTRACT:**

**Background**: Although there is growing evidence relating DNA repair to the modulation of CAG repeat expansion (CAGexp) diseases [1, 2, 3], not much is known about it in the spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD). We aimed to correlate functional variants in mismatch repair (MMR) genes *MLH1, MLH3, MSH2, MSH3, MSH6* and *PMS1* with AO in a clinically well-characterized SCA3/MJD cohort, compare their effects with those of *ATXN2*, and look for possible interactions.

**Methods:** Symptomatic carriers with CAGexp < 81 repeats and belonging to the SCA3/MJD cohort of Rio Grande do Sul, Brazil, were included. rs1799977 (*MLH1*), rs175080 (*MLH3*), rs2303425 (*MSH2*), rs2250063 (*MSH3*), rs1042821 (*MSH6*), rs3791767 (*PMS1*), rs1805323 (*PMS2*), and the major CAG allele at *ATXN2* were genotyped, as well as the CAG alleles at *ATXN3*. Regression analyses for the age at onset of gait ataxia (AOga) were done, using CAGexp, family and each genotype at a time as independent variables. Then subjects were studied through a dominant model for each genotype and for a CAGexp of 75 repeats, by univariate analysis of variance, to determine the changes in AOga. Interactions of markers that achieved significance were also tested, for a p of 0.05.

**Results**: Genotypic variability allowed *MSH3, MLH3, MLH1, MSH6, MSH2, PMS1,* and *ATXN2* to be studied in 386 SCA3/MJD patients recruited. Variants in *MLH1, MSH3, MSH6,* and *ATXN2* significantly changed the AOga. For instance, carrying rs1042821-G at *MSH6* delayed AOga for a mean (SEM) of 4.55 (2.31) and alleles of up to 26 repeats at *ATXN2* delayed it for 7.64 (6.87) years. Significant interactions were detected between *MSH6* and *MSH3* and *ATXN2*. The lack of any protective genotype in these pairs of genes seemed to be the underlying mechanism; additive effects were not apparent.

**Discussion**: We raised evidence that MMR protective variants at *MLH1, MSH3* and *MSH6*, plus *ATXN2*, delay AOga in SCA3/MJD. These findings suggest that somatic instabilities might participate in the pathogenetic process of this condition.

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