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Age at onset of gait ataxia in Spinocerebellar Ataxia type 3/ Machado-Joseph Disease is modulated by population-specific factors

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In spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD), the length of the CAG repeat expansion (CAGexp) in ATXN3 inversely correlates with age at onset of the first symptom (AOfs) and of gait ataxia (AOga). Accurately predicting AO in asymptomatic carriers is advantageous for both genetic counseling and research, and a model ("European formula" or EF) for AOga estimation was recently developed in Europe. The aim of this study was to test EF in a large SCA3/MJD cohort from South Brazil. EF underestimated the known AOga by an average of 10.41 years in 100 symptomatic patients. Similarly, 31/47 preclinical carriers were still asymptomatic at ages older than those predicted by EF (average error of 7.82 years). These differences led us to develop an adjusted equation ("Brazilian Formula" or BF) using regression models with parameters estimated based on the South Brazilian SCA3/MJD discovery cohort (n=147). We validated BF in two geographically distinct SCA3/MJD validation cohorts of patients from South Brazil (n=107) and Azores, Portugal (n=95). Indeed, BF was significantly superior than EF at predicting AOga in South Brazilians (mean prediction error: +2.15 vs. -9.35 years, respectively). However, BF overestimated AOga in Azoreans by an average of 14.06 years, while EF behaved significantly better, underestimating AOga in this group by only 2.55 years, on average. These results strongly suggest that AO in SCA3/MJD is co-determined by population-specific factors, and that carrier individuals from South Brazil with large ATXN3 expansions likely have protective factors that significantly delay AO. Palavras-chaves: Machado-Joseph Disease, spinocerebellar ataxia type 3, age at onset