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Gender equality in Machado-Joseph disease

Sir — In the April 1995 issue of *Nature Genetics*, Kawakami *et al.*[1] provided evidence for a gender effect in Machado-Joseph disease, a form of autosomal dominant cerebellar ataxia type I linked to chromosome 14q, which is allelic to spinocerebellar ataxia 3 (SCA3) (ref. 2). They analyzed 14 affected sib pairs of which seven were of different sexes and found that brothers develop symptoms about ten years earlier than sisters. This prompted us to look for a gender effect in our series of five sib pairs and six triplets of different sexes from 11 families with the MJD/SCA3 CAG expansion. We averaged the age at onset between sibs of the same sex in triplets. Mean ages at onset in brothers and sisters were not significantly different, 37.2 ± 11 (22–57) and 39.6 ± 15 (22–70), respectively. Onset in brothers occurred at a mean of –2.45 years earlier than in sisters but this was not significant ($P = 0.16$, paired t-test). The mean difference between the number of CAG repeats in males (72.8 ± 3) and females (73.5 ± 5) was also not significant (–0.64, $P = 0.35$). The difference between the actual age at onset and the expected age at onset, determined from the linear regression correlating age at onset and number of CAG repeats in 89 patients, was not significantly different in males (–0.6 ± 5 years) and in females (2.9 ± 7 years) from the discordant sibships.

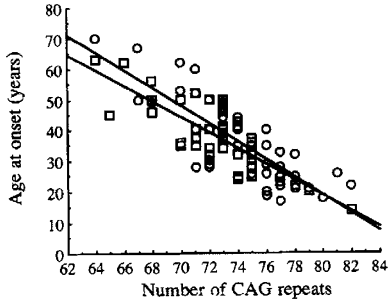

Fig. 1 Correlation between age at onset and the number of CAG repeats according to sex. Circles indicate women, squares indicate men.

We found no statistically significant differences between 41 and 48 affected men and women from 28 families with the MJD/SCA3 expansion. The mean age at onset was 38 ± 11 years for men and 36 ± 13 years in women, and the mean number of CAG repeats 72.6 ± 4 and 74.0 ± 4, respectively. The regression and correlation coefficients between age at onset and CAG repeat number were similar in men ($r = -0.82$; slope –2.61) and in women ($r = -0.79$; slope –2.79) (Fig. 1). Furthermore, the covariance analysis using the repeat number as the variant to control for its effect on age at onset was not significant. In these families, the number of CAG repeats accounts for approximatly 60% of the variability in age at onset, a value which is similar to that found in spinocerebellar ataxia 1 (SCA1) (ref. 3).

Our results indicate that gender has no sizeable effect on age at onset. Previous results suggesting a gender effect may be attributable to a bias due to the smaller number of sibs analyzed. Our finding is reinforced by the absence of a gender effect on age at onset in MJD in Brazilian families of Portuguese ancestry[4]. As yet unidentified genetic or environmental factors could be responsible for the residual age at onset variance in autosomal dominant cerebellar ataxias.

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Sir — Age at onset of Machado-Joseph disease (MJD) is inversely correlated with number of CAG repeats in the *MJD1* gene[5]. We have confirmed these results in a data set of 156 affected individuals from North America, Brazil and Portugal[6]. The number of CAG repeats accounts for 50% of the variation in age at onset suggesting other factors influence onset[6]. Kawakami *et al.*[1] recently proposed that gender and gene dosage affect onset age. Our studies suggest that gender has little effect, but that variation in onset age is partially accounted for by an effect common to sibships that is independent of CAG repeat length.

We found no significant difference in age at onset between males (38.1 ± 1.3) and females (37.4 ± 1.5)