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RAPID COMMUNICATION

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Transmission distortion of the mutant alleles in spinocerebellar ataxia

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Abstract Spinocerebellar ataxia type 1 and type 3 (SCA1, SCA3) are autosomal dominant neurodegenerative disorders caused by expanded CAG trinucleotide repeats in novel genes. In our collective of SCA1 and SCA3 families, we observed distortion of the Mendelian 1:1 segregation of the disease. The mutated alleles were preferentially transmitted by female carriers in SCA3, whereas a gender effect on clinical features such as age of onset was not obvious. The mechanism underlying segregation distortion remains to be established.

Introduction

Trinucleotide repeat disorders display several unique genetic and clinical features. For practical reasons one can divide this group into two subgroups (Ross 1995). Type 1 is caused by the expansion of CAG trinucleotides within the open reading frame of genes coding for polyglutamine blocks as in Huntington's disease (HD), spinobulbar muscular atrophy (SBMA), dentatorubropallidoluysian atrophy (DRPLA), spinocerebellar ataxia type 1 (SCA1) and Machado-Joseph disease (MJD). Type 2 is caused by elongated CTG, CCG or GAA repeats outside the open reading frame and affecting the transcription/translation efficiency of the respective gene. Most of the diseases caused by CAG trinucleotide expansion present with anticipation (except for SBMA, which shows variable severity), that is, an earlier age of onset with subsequent generations. This effect is caused by an expansion of the trinucleotide repeat during gametogenesis and is considered a hallmark of such dynamic mutations. The repeat length of the mutated allele is inversely correlated with the age of onset in affected patients. It remains an open question why expansions occur most frequently via maternal transmission in the fragile-X syndrome or in myotonic dystrophy (type-2 disorders), but through paternal transmission in type-1 disorders.

For spinocerebellar ataxias further unusual clinical and genetic features have been described. In a limited number of patients it has been shown that the gender of the affected person influences age of onset (Kawakami et al. 1995). At similar CAG repeat lengths, females were found to develop the disease approximately 5 years later than their male siblings. Other studies, however, did not confirm these findings (DeStefano et al. 1995; Dürr et al. 1995). Furthermore, Kawakami et al. (1995) provided evidence for the dosage of the mutated gene affecting the age of onset. This finding was somewhat surprising as homozygotes in HD do not present with an earlier age of onset than patients with a single affected allele (Wexler et al. 1987; Myers et al. 1989). It has also been observed that the numbers of affected offspring exceed those of unaffected offspring in DRPLA and MJD families (Ikeuchi et al. 1996), which excludes random segregation of alleles. To investigate such phenomena further in independent patients we analyzed German families with autosomal dominant spinocerebellar ataxia (ADSCA).

We and others have shown that spinocerebellar ataxia type 3 (SCA3) is caused by mutations in the MJD1 gene (Schöls et al. 1995a; Higgins et al. 1996) although in SCA3 characteristic features such as dystonia, bulging eyes and faciolingual fasciculations are rare (Schöls et al. 1995b). SCA3 is the most common cause of ADSCA in Germany and accounts for up to 50% of cases (Schöls et al. 1995a) whereas mutations in the ataxin-1 gene are responsible for the disease in about 10% of all ADSCA families investigated (Schöls et al. 1995c).

Here we analyzed SCA1 and SCA3 families for (1) gender differences affecting the age of onset, (2) distortion of random segregation of MJD and SCA1 alleles, and (3) whether there is an influence of the sex of the transmitting parent.

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Table 1 Transmission of mutant alleles to progeny in spinocerebellar ataxia type 1 (SCA1) and SCA3/MJD (Machado-Joseph disease). (*ns* = not significant)

Disorder and parent of origin	No. affected (male:female)	No. unaffected (male:female)	Total (male:female)	χ^2	Probability
SCA1					
Father	13 (5:8)	2 (1:1)	15 (6:9)	3.12	ns
Mother	10 (6:4)	2 (0:2)	12 (6:6)	1.68	ns
Total	23 (85%)	4 (15%)	27	6.11	$P < 0.05$
SCA3					
Father	45 (25:20)	40 (21:19)	85 (46:39)	0.05	ns
Mother	51 (30:21)	19 (11:18)	70 (41:39)	6.78	$P < 0.01$
Total	96 (62%)	59 (38%)	155	4.01	$P < 0.05$

Patients and methods

In total, the segregation patterns in four German SCA1 families with 27 children and nine SCA3 families with 155 parental transmissions were evaluated (Table 1). The diagnosis of SCA1 or SCA3 was confirmed for each pedigree by molecular genetic analysis. All individuals were included in this study. The diagnosis of affected or unaffected was assessed by molecular genetic determination of CAG repeat size (10 persons in SCA1 and 39 in SCA3), clinical examination (9 individuals in SCA3 families) by the same neurologist (L. S.), or by interviews (17 individuals in SCA1 and 107 individuals in SCA3). Patients with mutations in the MJD1 gene presented with the SCA3 phenotype. More details of the clinical data have been described previously (Schöls et al. 1995b).

Results

In order to estimate the overall influence of gender on the age of onset we calculated the average age of onset in males and females (Fig. 1) by analogy with the analysis of Dürr et al. (1995) and DeStefano et al. (1995). In men, the mean age of onset was 35.1 ± 11.2 years. The difference in the age of onset from that of the female patients (38.0 ± 9.1 years) is not significant ($P = 0.16$, unpaired *t*-test). The mean repeat size was identical with 72.3 ± 3.7 in males and 72.3 ± 3.2 in females.

To analyze the influence of the sex of sibs on the age of onset, Kawakami et al. (1995) compared affected sibs with similar CAG repeat sizes. Owing to the limited number of our SCA1 patients, a statistical analysis could not be performed. In the SCA3 pedigrees, we found sibs with identical expanded CAG repeat sizes and irregular influence of sex. In one sib pair, the affected sister showed symptoms 10 years earlier than her brother (age 37 vs 47 years, with a repeat length of 71). In another sib pair the brother showed an earlier age of onset (29 vs 42 years, 71 repeats).

The χ^2 test was applied to evaluate the gender effect of the transmitting parent under the null hypothesis of a 1:1 segregation ratio of unaffected to affected offspring. In the SCA1 pedigrees, 23 of 27 offspring (85%) inherited the affected alleles from their parents ($\chi^2 = 6.11$, $P < 0.05$). No significant influence of parental sex was found (Table 1). In SCA3, 96 offspring (62%) are affected or gene carriers, respectively ($\chi^2 = 4.01$, $P < 0.05$). In SCA3, a significant distortion in favor of transmission of the mutant alleles was observed in female meioses ($\chi^2 = 6.78$, $P < 0.01$).

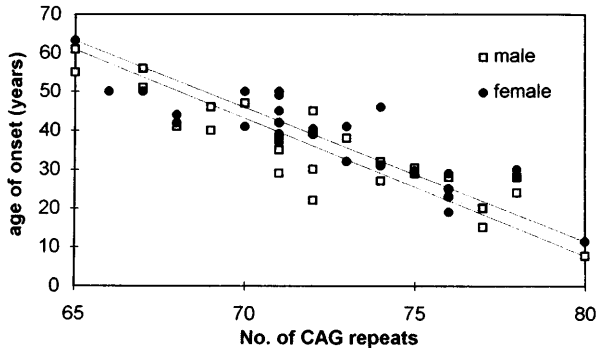

Fig. 1 Correlation between CAG repeat length and age of onset in male and female SCA3 patients. Regression curves are derived from the formula:
male: $x = 82.2–0.28 \times y$; $r = –0.8517$; $P < 0.0001$
female: $x = 83.3–0.29 \times y$; $r = –0.8109$; $P < 0.0001$
where x = number of CAG motifs and y = age of onset in years

Discussion

This study provides further evidence for distortion of the Mendelian 1:1 segregation of affected versus unaffected alleles in SCA3 families, and extends this finding to SCA1 pedigrees. In addition, a gender effect is evident in the maternal transmittance of SCA3, which is contrary to the observed distortion in paternal transmittance in Japanese MJD families (Ikeuchi et al. 1996). In principle, one could assume selective advantages during maturation of germ cells harboring the elongated protein. Studies of ataxin-3 mRNA showed predominant expression in testis (I. Schmitt and O. Riess, unpublished) although detailed studies of the individual cell types have not yet been performed. In HD, in situ hybridization analysis provided evidence for enhanced expression of huntingtin mRNA in

spermatocytes but not in maturing spermatids (Schmitt et al. 1995). However, sperm analysis did not indicate an increased frequency of sperm cells harboring expanded HD alleles (Leeflang et al. 1995). If this holds true for SCA3 one must assume selection advantages for the fertilized zygote around the time of implantation or soon thereafter. It remains open, why segregation distortion is being observed during maternal transmittance in German families but in paternal inheritance in Japanese pedigrees. Further discussion is also warranted on the question why mutations in the same gene cause distinct phenotypes in different populations. One could assume that thus far unidentified polymorphisms in the ataxin-3 gene are responsible for these features. Furthermore, polymorphisms in interacting proteins such as HAP1 in HD (Li et al. 1995) or GAPDH in HD and DRPLA (Burke et al. 1996) could account for the clinical differences. The conclusion of Ikeuchi et al. (1996) that a common molecular mechanism might underlie segregation distortion and meiotic instability in males does not apply to our SCA families. Further studies should clarify whether these genetic features are common to all CAG trinucleotide disorders including HD.

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