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Non-Mendelian Transmission in Dentatorubral-Pallidoluysian Atrophy and Machado-Joseph Disease: The Mutant Allele Is Preferentially Transmitted in Male Meiosis

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Summary

Autosomal dominant dentatorubral-pallidoluysian atrophy (DRPLA) and Machado-Joseph disease (MJD) are neurodegenerative disorders caused by CAG trinucleotide repeat expansions. An inverse correlation of age at onset with the length of the expanded CAG trinucleotide repeats has been demonstrated, and the intergenerational instability of the length of the CAG trinucleotide repeats, which is more prominent in paternal than in maternal transmissions, has been shown to underlie the basic mechanisms of anticipation in DRPLA and MJD. Our previous observations on DRPLA and MJD pedigrees, as well as a review of the literature, have suggested that the numbers of affected offspring exceed those of unaffected offspring, which is difficult to explain by the Mendelian principle of random segregation of alleles. In the present study, we analyzed the segregation patterns in 211 transmissions in 24 DRPLA pedigrees and 80 transmissions in 7 MJD pedigrees, with the diagnoses confirmed by molecular testing. Significant distortions in favor of transmission of the mutant alleles were found in male meiosis, where the mutant alleles were transmitted to 62% of all offspring in DRPLA ($\chi^2 = 7.69$; $P < .01$) and 73% in MJD ($\chi^2 = 6.82$; $P < .01$). The results were consistent with meiotic drive in DRPLA and MJD. Since more prominent meiotic instability of the length of the CAG trinucleotide repeats is observed in male meiosis than in female meiosis and meiotic drive is observed only in male meiosis, these results raise the possibility that a common molecular mechanism underlies the meiotic drive and the meiotic instability in male meiosis.

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Introduction

Dentatorubral-pallidoluysian atrophy (DRPLA) (MIM 125370) and Machado-Joseph disease (MJD) (MIM 109150) are neurodegenerative disorders that show autosomal dominant inheritance and are characterized clinically by ataxia as a cardinal feature accompanied by various combinations of neurological signs and symptoms (Rosenberg et al. 1976; Naito and Oyanagi 1982). The causative mutations for DRPLA and MJD have been identified as unstable expansions of CAG trinucleotide repeats at 12pter-p12 and 14q32.1, respectively (Kawaguchi et al. 1994; Koide et al. 1994; Nagafuchi et al. 1994). To date, unstable expansions of CAG repeats have also been identified as the causative mutations for Huntington disease (Huntington's Disease Collaborative Research Group 1993), spinal and bulbar muscular atrophy (La Spada et al. 1991), and spinocerebellar ataxia type 1 (Orr et al. 1993).

These diseases exhibit unusual clinical and genetic features, namely, both variable ages at onset and considerable phenotypic heterogeneities within the same pedigrees. Of particular interest is the genetic anticipation, i.e., acceleration of age at onset and increased severity of the disease in successive generations. It is interesting to note that paternal transmissions were found to result in more prominent acceleration of age at onset (25.6 ± 2.4 years in DRPLA, 15.4 ± 2.5 years in MJD; mean ± SEM) and greater intergenerational increase in the number of CAG repeat units (+5.8 ± 0.9 repeat units in DRPLA, +3.2 ± 0.8 repeat units in MJD) than did maternal transmissions (acceleration of age at onset: 14.0 ± 4.0 years in DRPLA, 6.9 ± 2.0 years in MJD; and intergenerational increase: +1.3 ± 1.6 repeat units in DRPLA, +1.2 ± 0.4 repeat units in MJD) (Ikeuchi et al. 1995*b*; Takiyama et al. 1995). Recent discoveries of the causative mutations for these diseases revealed that these unusual clinical and genetic features are intimately related to the length instability of the CAG trinucleotide repeat. It has been demonstrated that intergenerational increases in the length of the expanded CAG trinucleotide repeat result in acceleration of ages

at onset and phenotypic variability of these diseases (Ikeuchi et al. 1995*a*; Komure et al. 1995; Maruyama et al. 1995; Takiyama et al. 1995).

Our previous observations on DRPLA and MJD pedigrees, as well as a review of the literature, have suggested that the numbers of affected offspring exceed those of unaffected offspring, which is difficult to explain by the Mendelian principle of random segregation of alleles (Ikeuchi et al. 1995*a*; Takiyama et al. 1995). Prompted by the idea that unusual genetic mechanisms may be involved in the segregation distortion of the mutant alleles of DRPLA and MJD, we performed detailed segregation analyses. Here we report that there is a significant segregation distortion of expanded alleles, which suggests that a novel mechanism is involved in the meiotic segregation of these mutant alleles.

Subjects and Methods

We analyzed 211 transmissions in 24 DRPLA pedigrees (Fj, Fs, Fw, In, Is, Km, Ks, Ky, Mr, Ng, Nk, Nm, Oh, Ok, Sa, Se, Sh, Sk, Tc, Td, Tk, Tu, Uj, and Wt) and 80 transmissions in 7 MJD pedigrees (Ya, Yg, On, Su, Hi, Ko, and Ch) (Ikeuchi et al. 1995*a*; Takiyama et al. 1995). The diagnosis of DRPLA or MJD was confirmed for each family, on the basis of molecular testing. In the 211 transmissions in the 24 DRPLA pedigrees, we identified 114 affected individuals and 97 unaffected individuals. We included everyone at risk in each pedigree in this study. Of the 97 unaffected individuals, 54, 37, and 6 were considered to be unaffected, on the basis of clinical examinations by certified neurologists, interviews, or molecular testing, respectively. The ages at examination for affected and unaffected individuals in the DRPLA pedigrees ranged from 11 to 79 years and 8 to 76 years (mean = 43.2 years), respectively. In the 80 transmissions in the seven MJD pedigrees, we identified 50 affected individuals and 30 unaffected individuals. Of the 30 unaffected individuals, 26 were confirmed not to carry the mutant alleles, either by linkage analysis or by molecular analysis of the CAG repeats of the *MJD1* gene. The remaining four individuals were considered to be unaffected, on the basis of clinical examinations by certified neurologists. The ages at examination for affected and unaffected individuals in the MJD pedigrees ranged from 6 to 72 years and 7 to 77 years (mean = 45.5 years), respectively.

The χ^2 test was applied as a test of goodness of fit of a model to the obtained data under the null hypothesis of a 1:1 segregation ratio of offspring born to affected parents. Evidence of segregation distortion that differs in accordance with the sex of the transmitting parent was tested using Fisher's exact test. Multiple stepwise logistic regression was performed in which the dependent variable was the affected status of the offspring and the predictors were the sex of the parent and the sex of the offspring. Statistical analyses were performed using SAS software, release 6.08.

Results

Table 1 summarizes the numbers of affected and unaffected offspring of a DRPLA- or MJD-affected father or mother. In DRPLA, a significant distortion in favor of transmission of the mutant alleles was found in male meiosis; the mutant alleles were paternally transmitted to 63% of all offspring in the DRPLA pedigrees ($\chi^2 = 7.69$; $P < .01$). The distortion is also statistically significant at the 5% level after the correction of type 1 error for multiple comparison of three tests in table 1 (Bonferroni's procedure) (Hurst et al. 1995). No significant segregation distortion was detected among offspring born to affected mothers. To determine whether sex-specific ratio distortion existed, we applied Fisher's exact test and obtained statistically significant segregation distortion ($P = .048$, two-tailed) for the DRPLA pedigrees. There were no statistically significant differences in the distribution of the numbers of sons and daughters produced by fathers compared with that of sons and daughters produced by mothers ($\chi^2 = 0.11$).

Multiple stepwise logistic regression analysis demonstrated that the gender of the DRPLA-affected parent, but not the gender of the offspring, contributed significantly to the affected status of the offspring ($P < .01$). An interaction term between the gender of the affected parent and the gender of the affected offspring did not indicate significant contribution to the affected status of offspring.

In MJD, a quite similar phenomenon was observed, as shown in table 1. In male meiosis, the mutant alleles were transmitted to 73% of all offspring ($\chi^2 = 6.82$; $P < .01$). The distortion is also statistically significant after the correction of type 1 error at the 5% level (Hurst et al. 1995). Such segregation distortion was not detected in female meiosis. In Fisher's exact test, however, the segregation distortion did not reach statistical significance for MJD segregation ($P = .196$, two-tailed). Multiple stepwise logistic regression analysis using the gender of the affected parent, the gender of the offspring, and the interaction term did not demonstrate a statistically significant effect on the affected status of the offspring in MJD ($P = .09$).

Discussion

The present study demonstrated that there are significant segregation distortions as judged by χ^2 analysis in the transmissions of both mutant DRPLA and MJD alleles. These results raise the possibility of the presence of meiotic drive at DRPLA and MJD loci. Since the best evidence for the presence of meiotic drive is sex-specific

Table 1

Transmission of Mutant Alleles to Progeny in DRPLA and MJD

Disorder and Parent of Origin	No. Affected (%) [male:female]	No. Unaffected (%) [male:female]	Total [male:female]	χ^2	Probability	Significance after Correction
DRPLA:						
Male	78 (63) [37:41]	47 (37) [27:20]	125 [64:61]	7.69	$P < .01$	Significant at the 5% level
Female	36 (42) [22:14]	50 (58) [24:26]	86 [46:40]	2.28	$.1 < P < .2$	ns
Total	114	97	211	1.37	$.2 < P < .3$	ns
MJD:						
Male	24 (73) [9:15]	9 (27) [4:5]	33 [13:20]	6.82	$P < .01$	Significant at the 5% level
Female	26 (55) [13:13]	21 (45) [10:11]	47 [23:24]	.53	$.3 < P < .5$	ns
Total	50	30	80	5.00	$.01 < P < .05$	ns

NOTE.—ns = not significant.

distortion, we performed Fisher's exact test, which revealed a statistically significant distortion at the DRPLA locus ($P < .05$). Furthermore, multiple logistic regression analysis demonstrated that only the gender of the DRPLA-affected parent contributed significantly to the segregation distortion ($P < .01$). In the case of MJD, however, the segregation distortion did not reach statistical significance as determined by either Fisher's exact test ($P = .196$) or multiple logistic regression analysis ($P = .09$).

The present results therefore provide evidence of meiotic drive in DRPLA and only marginal evidence of meiotic drive in MJD. In the case of DRPLA, we analyzed 211 transmissions, while in the case of MJD, we analyzed only 80 transmissions. The relatively small number of observations for MJD might account for the weakness of the evidence of meiotic drive in MJD. Furthermore, it should be noted that our analysis included 91 individuals who were judged not to be affected with DRPLA and 4 individuals who were judged not to be affected with MJD, on the basis of either clinical examination or interview. Since 39% and 50% of the individuals in the DRPLA and MJD pedigrees, respectively, were <40 years of age there remains the possibility that some of these individuals carry the mutant genes. Therefore, the segregation distortion might in fact be more prominent, since in our analysis we might have underestimated the number of affected individuals in these pedigrees. To conclude unequivocally that meiotic drive occurs in MJD, we need to analyze a larger number of transmissions.

Meiotic drive has been identified in various models including the segregation-disorder system in *Drosophila* (Lyttle 1993), the spore-killer system in *Neurospora* (Raju and Perkins 1991), and the mouse *t* haplotypes (Silver 1993), as well as in human diseases including retinoblastoma (Munier et al. 1992), split hand/split foot disease (Jarvik et al. 1994), and cone-rod retinal dystrophy (Evans et al. 1994).

Gennarelli et al. (1994) recently reported that affected fathers more frequently transmit the mutant alleles than the wild-type alleles to their offspring in myotonic dystrophy, a disease caused by CTG trinucleotide repeat expansion. Furthermore, Carey et al. (1994, 1995) reported that males, even in the case of normal alleles, more frequently transmit the larger alleles of normal length than the smaller alleles of normal length to their offspring. Although the validity of the statistical analyses has been disputed (Hurst et al. 1995), these studies raise the possibility that meiotic drive is a common phenomenon in diseases caused by trinucleotide repeat expansions.

Preferential paternal transmission of the mutant DRPLA and MJD alleles should be considered in genetic counseling, because the frequency of inheritance of mutant alleles in paternal transmission is much higher than expected on the basis of the Mendelian segregation law. The unusual genetic features of greater intergenerational increase in size of expanded alleles in male meiosis compared with that in female meiosis and more frequent transmission of expanded alleles compared with that of normal alleles in male meiosis raise the intriguing possibility that a common molecular mechanism underlies the segregation distortion and the meiotic instability of the CAG repeats in male meiosis.

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