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Non-Mendelian transmission at the Machado-Joseph disease locus in normal females: preferential transmission of alleles with smaller CAG repeats

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Abstract

Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3, is a neurodegenerative disorder which is associated with a CAG repeat expansion in the MJD1 gene on chromosome 14q32.1. A recent study reported an excess of transmission of disease chromosomes relative to normal chromosomes from affected fathers, while this phenomenon was not observed in female meioses. These data were compatible with meiotic drive. We investigated the transmission of alleles with larger versus smaller CAG repeat numbers in the MJD1 gene in normal heterozygotes from the 40 CEPH families. Our data suggest that there was no segregation distortion in male meioses, while the smaller CAG allele was inherited in 57% of female meioses ($p<0.016$). The pattern of inheritance of smaller versus larger CAG alleles at this locus was significantly different when male and female meioses were compared ($p=0.0139$). While previous data suggest that meiotic drive may be a feature of certain human diseases, including the trinucleotide diseases MJD, myotonic dystrophy, and dentatorubral-pallidoluysian atrophy, these data are compatible with meiotic drive also occurring among non-disease associated CAG sizes.

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Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3, is an autosomal dominant neurodegenerative condition which results in cerebellar ataxia as a primary feature and various other neurological signs and symptoms. Recently, this disease has been shown to be associated with abnormal expansions of a CAG trinucleotide repeat in the MJD1 gene localised at 14q32.1.[1] Normal chromosomes have 14 to 44 repeats while disease chromosomes have 60 to 84 repeats.[2]

The CAG repeats in MJD, like those in the Huntington's disease, spinocerebellar ataxia type 1, Kennedy's disease (androgen receptor), and dentatorubral-pallidoluysian atrophy genes, are thought to be translated into a polyglutamine tract. These diseases share a number of clinical features. The number of CAG repeats on mutant chromosomes correlates with increasing severity of disease or decreasing age of onset of symptoms. Repeat number on disease chromosomes tends to increase in successive generations, particularly when transmitted through the male line. This leads to the phenomenon of anticipation, where the age of onset in affected offspring tends to be lower than that in their parents.[3]

Recently, Ikeuchi *et al*[4] examined families with MJD and found that 73% of children from affected males carried the mutant allele ($\chi^2=6.82$, $p<0.01$). This deviation from 1:1 expectation was not observed in female meiosis. These data confirmed previous clinical observations which suggested that there was an excess of affected versus unaffected offspring in families with this disease and were compatible with meiotic drive, a form of non-Mendelian inheritance that results from the differential success of alleles at a specific locus in heterozygotes at the gametic stage. All known examples of meiotic drive are sex specific and occur either in males or females, but not both.[5] Thus, the observation of the inheritance of an excess of mutant MJD alleles from affected fathers cannot be easily explained by increased viability of zygotes, since this explanation would also result in the segregation distortion being apparent in female meioses.

Since we have a particular interest in trying to understand the processes underlying the evolution of these trinucleotide repeat disorders, we investigated this phenomenon in normal subjects from the CEPH families. In offspring of informative meioses of normal heterozygous females, there was preferential transmission of MJD1 alleles with smaller CAG repeat numbers. This phenomenon was not observed in males and there was a significant difference in the transmission of larger versus smaller normal repeats in male compared to female meioses.

Methods

CAG repeat sizes in the CEPH (Centre d'Etude du Polymorphism Humaine) families were determined as described previously.[1 6] At each informative meiosis in heterozygous males or females, we determined whether the MJD1 allele with larger or smaller CAG repeats was transmitted. Statistics were performed using SPSS software (SSPC, Chicago, Illinois).

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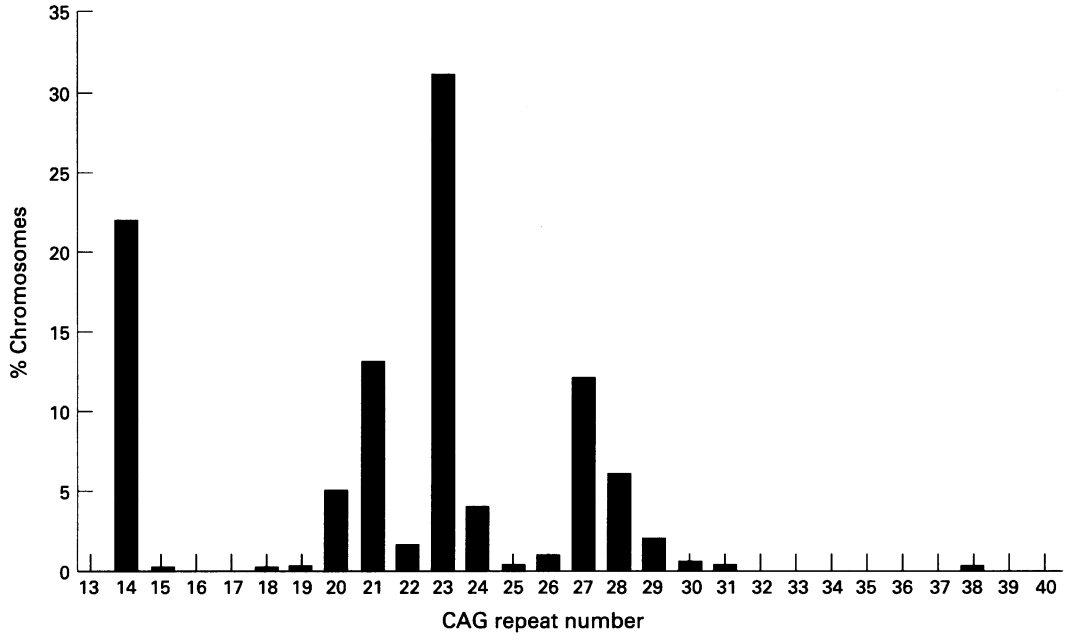

Figure 1 CAG repeat size distribution in unrelated chromosomes from subjects in the CEPH families.

Results

The transmissions of the MJD repeats were analysed in the 40 CEPH families. The allele frequency distributions from unrelated subjects from these families shared two modes at 14 and 23 repeats with the East Anglians, Finns, Asian Indians, and Sardinians which we have examined previously (fig 1).[6]

We analysed offspring and their parents to see if there was any deviation from a 1:1 expectation of inheriting alleles with either a smaller or larger CAG repeat length in informative meioses of heterozygotes (table 1). This analysis was determined for male and female meioses separately. Since all previous examples of meiotic drive have been sex specific,[5] there was no a priori reason to test the female and male meioses together in one group. The statistical significance of any deviations was determined using two tests: χ^2 statistics assuming a null expectation of a 1:1 ratio[4 5] and the precise binomial probability. No significant deviation from the 1:1 expectation was seen in male meioses but heterozygous females transmitted their smaller allele in 166 of 290 informative meioses (57%) (χ^2=6.08, p=0.01365; p=0.0158, precise binomial probability, two tailed).

The segregation pattern of alleles with larger versus smaller CAG repeat lengths from female and male meioses was significantly different (χ^2=6.04, p=0.014). After Bonferroni correction for three tests, which reduces the p value to 0.0166, these data and the deviation from a 1:1 expectation of inheriting alleles with either a smaller or larger CAG repeat length in informative meioses of heterozygous females remain significant at the 95% level.

Table 1 Segregation analysis of larger v smaller MJD1 CAG repeat sizes in informative meioses in normal heterozygotes. Deviation from 1:1 was analysed both with χ^2 test and two tailed binomial analysis. The segregation of larger v smaller alleles in males compared to females was significantly different (χ^2 = 6.04, 1 df, p = 0.014)

	Larger allele transmitted	*Smaller allele transmitted*	*χ^2 assuming 1:1 segregation*	*p (χ^2)*	*p for precise binomial*
Male parent	143	126	0.54	> 0.5	0.328
Female parent	124	166	6.08	0.0137	0.0158

Discussion

Analysis of segregation patterns of the MJD CAG repeats in normal heterozygous female meioses suggests that there is a greater likelihood of passing on smaller than larger repeat lengths. Our data are compatible with meiotic drive, since no such difference was observed in male meioses and the pattern of inheritance of larger versus smaller alleles was significantly different in males and females.

Our findings at this locus appear to differ from those reported by Ikeuchi *et al*,[4] who reported an excess of transmission of large disease associated alleles versus normal alleles from affected fathers but not affected mothers.[4] However, we believe that the putative effect of mutant alleles compared to normal alleles on gamete survival may be different from any effects between normal alleles of different length.

Meiotic drive has been suggested for a variety of human diseases[4] including CAG/CTG trinucleotide repeat diseases. Affected fathers with dentatorubral-pallidoluysian atrophy and myotonic dystrophy tend to pass on their mutant allele more frequently, and this phenomenon was not apparent in affected mothers. We are not aware of a confirmed description of this phenomenon in humans which affects non-disease alleles. Although Carey *et al*[7] reported preferential transmission of larger normal alleles versus smaller normal alleles at the myotonic dystrophy CTG repeat locus, reanalysis of their data by Hurst *et al*[5] casts doubts on the validity of their conclusions. We have also analysed the CAG repeats at the Huntington's disease locus for abnormal segregation in normal families and found no evidence for segregation distortion.[8]

Our results may be the first example of meiotic drive in humans which does not involve a disease-causing allele. One can only speculate

about possible mechanisms which could underlie such a phenomenon. It is possible that the number of CAG repeats in the normal size range at the MJD locus is associated with subtle quantitative effects on gene function in a manner analogous to that described for the androgen receptor, where transactivational competence is inversely proportional to repeat number.[9] Such an effect may favour female germ cells with smaller repeat numbers in heterozygotes. However, we believe that our findings should be interpreted with some caution. Although the data remain significant after correction for multiple tests, they may still represent a chance phenomenon. It is also possible that other groups have investigated this phenomenon and have not reported negative findings. Thus, these findings should be replicated in an independent large set of families.

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