Mendelian segregation of normal CAG trinucleotide repeat alleles at three autosomal loci

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Abstract

Segregation ratio distortion (SRD) with preferential transmission of expanded CAG alleles has been reported in Machado-Joseph disease (MJD/SCA3), spinocerebellar ataxia type I (SCA1), and dentatorubral-pallidoluysian atrophy (DRPLA). We have examined the transmission frequencies of alleles in normal heterozygotes at these disease loci in 377 pairs of twins and their parents and find no evidence for SRD.

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Diseases caused by unstable expansions in trinucleotide repeat sequences display genetic anticipation and at a molecular level are characterised by varying degrees of sex dependent meiotic and postzygotic mitotic instability.[1] Recent reports have also shown that in at least some of these conditions there is evidence for non-mendelian segregation frequencies, such that the normal and disease alleles are not transmitted to offspring in a 1:1 ratio. The segregation ratio distortion (SRD) occurs upon transmission from the mother or father or from both parents depending on the study considered. Ikeuchi *et al*[2] found that the mutant allele in males with Machado-Joseph disease (MJD/SCA3) was transmitted to 73% of offspring, while 62% of the offspring of males with dentatorubral-pallidoluysian atrophy (DRPLA) inherited the disease allele. Reiss *et al*[3] in a smaller series of patients reported transmission of the expanded spinocerebellar ataxia type I (SCA1) allele to 13 of 15 offspring of affected males and 10 of 12 offspring of affected females. Reiss *et al*[3] also reported transmission of the expanded SCA3/MJD allele to 51 of 70 offspring of affected females, but transmission of the expanded SCA3/MJD allele to only 45 of 85 offspring of affected males (not different from the expected 1:1 in mendelian segregation). Rubinsztein and Leggo[4] expanded these observations by examining transmission ratios of normal sized alleles at the MJD/SCA3 locus in CEPH pedigrees. They found that males transmitted the larger allele 143 times compared with 126 for the smaller allele ($p>0.05$), whereas females transmitted the larger only 124 times in 290 meioses ($p=0.0137$). Teague *et al*[5] have recently examined normal, intermediate, pre- and full mutation alleles at both the FRAXA and FRAXE loci and found evidence against segregation distortion. They also critically reviewed the data on segregation distortion, including the conflicting data on myotonic dystrophy,[6–10] and commented that they "remain skeptical".[5]

We are interested in the transmission characteristics of repeat sequences within the normal range as a means of exploring the possible mechanisms by which these disorders arise and are maintained in the population. We have used adolescent twins and their parents to examine the transmission characteristics of alleles at the MJD/SCA3, SCA1, and DRPLA loci in normal heterozygotes.

CAG repeat lengths were analysed on an ABI Genescan system following multiplex PCR amplification of DNA from 377 pairs of adolescent twins and their parents. The twins (all white) had previously been recruited to participate in a longitudinal study of the development of melanocytic naevi (moles). Informed consent was received from all subjects. Zygosity was diagnosed by typing eight highly polymorphic DNA microsatellite markers (independently of the markers analysed in this present study) and three blood groups (ABO, MNS, and Rh) in the twins and in most cases both parents. Data were analysed by goodness of fit chi-square under the null hypothesis of a 1:1 segregation ratio for the transmission of the larger and the smaller allele. Monozygotic twins (counted as one meiosis) and dizygotic twins (two meioses) were analysed separately and subsequently as a pooled data set. Data were analysed separately by sex of parent and jointly, combining male and female meioses.

The results are summarised in tables 1, 2, and 3. There is no evidence for segregation ratio distortion in the transmission of 209 paternal and 224 maternal informative meioses at the MJD/SCA3 locus (mean difference between alleles, six repeats, range 1-20), in 244 paternal and 285 maternal informative meioses at the DRPLA locus (mean difference between alleles, four repeats, range 1-13) and in 283 paternal and 322 maternal informative meioses at the SCA1 locus (mean difference between alleles, two repeats, range 1-9). Heterogeneity

Table 1 Frequency of transmission of the larger and smaller alleles at the Machado-Joseph disease locus

	Allele transmitted					
Meiosis	*Larger*	*Smaller*	*Not informative*	*Total typed*	*χ^2 assuming 1:1 segregation*	*p (χ^2)*
MZ						
Paternal	23	31	18	72	1.158	0.276
Maternal	28	32	21	81	0.267	0.606
DZ						
Paternal	75	80	44	199	0.161	0.688
Maternal	78	86	55	219	0.390	0.532
Total						
Paternal	98	111	62	271	0.809	0.368
Maternal	106	118	76	300	0.643	0.423

Table 2 Frequency of transmission of the larger and smaller alleles at dentatorubral-pallidoluysian atrophy disease locus

	Allele transmitted					
Meiosis	*Larger*	*Smaller*	*Not informative*	*Total typed*	*χ^2 assuming 1:1 segregation*	*p (χ^2)*
MZ						
Paternal	35	30	19	84	0.134	0.714
Maternal	32	32	34	98	0	1
DZ						
Paternal	92	87	75	254	0.140	0.709
Maternal	102	119	74	295	1.308	0.253
Total						
Paternal	127	117	94	338	0.410	0.522
Maternal	134	151	108	393	1.014	0.314

Table 3 Frequency of transmission of the larger and smaller alleles at the spinocerebellar ataxia type 1 disease locus

	Allele transmitted					
Meiosis	*Larger*	*Smaller*	*Not informative*	*Total typed*	*χ^2 assuming 1:1 segregation*	*p (χ^2)*
MZ						
Paternal	31	29	28	88	0.067	0.796
Maternal	35	30	38	103	0.385	0.535
DZ						
Paternal	114	109	108	331	0.112	0.738
Maternal	133	124	100	357	0.315	0.574
Total						
Paternal	145	138	136	419	0.173	0.677
Maternal	168	154	138	460	0.609	0.435

between sexes, the hallmark of meiotic drive, is not seen at any of the loci studied. There is no difference in the segregation ratios between MZ and DZ twins. All monozygotic twins tested showed concordance for each of the three loci (data not shown) so there was no evidence for postzygotic instability.

Our analysis provides no evidence for non-mendelian transmission at the MJD/SCA3, SCA1, or DRPLA loci in normal subjects. Our study therefore does not support the findings of Rubinsztein and Leggo,[4] who reported a significant difference between males and females at the MJD locus where the smaller CAG allele was transmitted by females to 57% of their offspring (p=0.0137).

It is difficult to compare our findings from normal alleles with alleles in the disease range.[2 3] It cannot be assumed that they would necessarily behave in the same way at meiosis with respect to segregation, just as we know they do not behave in the same way in their stability (or lack of it). Our study does not address the issue of segregation distortion in the transmission of disease versus normal alleles.

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