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FRAXA and FRAXE: Evidence against segregation distortion and for an effect of intermediate alleles on learning disability

(fragile X/trinucleotide repeats)

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ABSTRACT **There have been several claims of segregation distortion (meiotic drive) for loci associated with diseases caused by trinucleotide repeats, leading us to test for this phenomenon in a large study of the X-linked loci FRAXA and FRAXE. We found no evidence of meiotic drive in females and no convincing evidence in males, where the limitation of risk to daughters creates a testing bias for alleles of interest. Alleles for pre- and full mutation, intermediate alleles, and common alleles were analyzed separately, with the same negative results that are extended in the discussion to claims of meiotic drive for other diseases. On the other hand, an excess risk of learning difficulties was confirmed for intermediate FRAXA alleles (relative risk, 2.58 ± .74) and suggested for intermediate FRAXE alleles. The penetrance of learning difficulty is low, the risk being estimated as .039 for FRAXA common alleles and .101 for intermediate alleles. Because of their lower gene frequency, full mutations are a less frequent cause of learning difficulty than intermediate alleles, which contribute .0020 to total prevalence and .0012 to attributable prevalence of learning difficulty.**

Meiotic drive, or segregation distortion, is a rare and incompletely understood phenomenon resulting in a breach of Mendel's second law and inheritance of an excess, and often a very large excess, of one class of gamete (1). Several reports in man, involving a number of different autosomal loci, have suggested preferential inheritance of one class of gamete, generally that carrying the mutant allele, from parents of one sex but not the other (e.g., refs. 2–4). These claims of segregation distortion usually are based on small numbers of observations and, where the observations are reported in sufficient detail, often can be seen to be the result of failure to correct for ascertainment bias.

Recently, there have been a number of papers suggesting the occurrence of segregation distortion in the transmission of loci associated with diseases caused by trinucleotide repeat expansions. Because this class of mutation is novel and does not obey the rules of Mendelian inheritance in a number of respects, it might also defy Mendel's law on segregation. The most persistent reports of meiotic drive in a trinucleotide repeat disease have been associated with myotonic dystrophy. Carey *et al.* (5) reported that among normal individuals with one allele at the upper end of the normal range (≥19 repeats), the large allele was selectively transmitted during male, but not female, meiosis. This suggested to the authors that transmission favoring large and perhaps more mutable alleles was a mechanism for maintaining myotonic dystrophy in the population in spite of its reduced reproductive fitness. Gennarelli *et al.* (6) reported a similar excess of individuals with myotonic dystrophy expansions in the affected range among children of affected parents, the excess being particularly marked in children of affected males. However, both these observations were criticized on statistical grounds by Hurst *et al.* (7). More recently Chakraborty *et al.* (8), analyzing myotonic dystrophy alleles in the normal size range in a series of Centre d'Étude du Polymorphisme Humain panel pedigrees, found evidence of preferential transmission of the large alleles during female meiosis although no such segregation distortion was found among male meioses. Finally, Leeflang *et al.* (9) studied individual spermatozoa from three men, each of whom had one large myotonic dystrophy allele with a repeat number greater than 19. In no instance did they find a transmission ratio significantly different from 0.5. Ikeuchi *et al.* (10) claimed segregation distortion in both dentatorubral-pallidoluysian atrophy (DRPLA) and Machado–Joseph disease with preferential transmission of the large alleles following male, but not female, meiosis in both diseases. In these analyses, alleles in the pathological size range were studied.

During a population study of two X-linked trinucleotide repeat diseases, FRAXA and FRAXE, we made an unexpected observation. Alleles in the intermediate and premutation size range, formerly thought to have no phenotypic effect because they are associated with normal levels of cellular protein in lymphocytes, were observed more often among the study population of boys with learning difficulties than among our control population of X chromosomes, namely the maternal X chromosome not transmitted to the son with learning difficulties (11). Formally, this result could be explained by differential transmission of the larger maternal allele, by increased risk of learning difficulties among carriers of intermediate alleles, by linkage disequilibrium between one or more genes causing learning difficulties, and a haplotype associated with intermediate alleles or by a type I error. Because we wanted to investigate this observation in more detail and because none of the claims for segregation distortion in man is conclusive, we decided to undertake (*i*) a segregation analysis of both FRAXA and FRAXE families with pre- and full-mutation alleles; (*ii*) a segregation analysis of families with intermediate-sized FRAXA and FRAXE alleles to determine whether the excess of such alleles among boys with special educational needs could be attributed to meiotic drive; (*iii*) a segregation analysis of heterozygotes in the common size range for FRAXA or FRAXE alleles; and (*iv*) a critical appraisal of the evidence for meiotic drive in man with special emphasis on trinucleotide repeats.

MATERIAL

Our material came from two sources, the first of which was a large, population-based molecular survey of FRAXA and

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Abbreviations: NTM, normal transmitting males; RR, relative risk.

Table 1. Segregation of FRAXA full- and premutation alleles in offspring of carrier mothers

Selection	Null hypothesis, $p = 0.5$			ML estimate,	Equivalent meioses	
	ML score, U_p	Information, K_{pp}	χ^2_1	p̂	Carrier	Total
Complete	8.0	192.0	0.33	.542	26	48
Incomplete ($\hat{\pi} = .141$)	−22.8	511.6	1.02	.455	58	128
Total	−14.8	703.6	0.31	.479	84	176

In Tables 1–3 and 5 the symbols are defined as follows (14): $\hat{\pi}$ is the maximum likelihood (ML) estimate of the ascertainment probability for sibship under incomplete selection; U_p is the maximum likelihood score under the null hypothesis H_0 that the segregation frequency is $p = .5$; K_{pp} is the amount of information corresponding to U_p; $\chi^2_1 = U_p^2/K_{pp}$ is a chi square with 1 degree of freedom testing H_0; and $\hat{p}$ is the maximum likelihood estimate of the segregation frequency. Equivalent meiosis are for a binomial distribution of pn affected in a sample of size $n = K_{pp}/4$, which gives the same value of χ^2_1.

FRAXE in boys with learning difficulties in Wessex and their mothers (11). Large alleles were classified as intermediate (FRAXA 41–60; FRAXE 31–60), premutation (FRAXA and FRAXE 61–200 and unmethylated) or full mutation (FRAXA and FRAXE ≥200 repeats and methylated). All other alleles were regarded as common. Complete family studies were undertaken on all large alleles whether they were ascertained first in a boy with learning difficulties or in his mother's control chromosome, or in other chromosomes ascertained as a result of family studies already ongoing under this protocol.

The second source of material was diagnostic pedigrees ascertained through probands, with learning difficulties referred to the Wessex Regional Genetic Service. Whenever a pre- or full mutation was found, complete family studies were undertaken. All available members of families in which a pre- or full mutation for FRAXA or FRAXE was segregating were tested for the size of both FRAXA and FRAXE alleles, in the course of which some intermediate alleles were ascertained. Thus, although the majority of probands in the diagnostic material were children with learning difficulties, occasionally other alleles whose segregation was of interest were found in cognate or affinal relatives who were therefore the probands for that particular allele.

METHODS

FRAXA. Most full mutations are seen to be descended from premutations, and so these two classes were pooled in segregation analysis as phenotype PF. We first compared the segregation of PF with that of all other alleles, taking PF as affected. A proband is defined as an individual with PF ascertained because of mental impairment, apparently independently of affected relatives. An ancestral proband is a carrier parent of a proband or another ancestral proband (12, 13). Because every sibship is from a carrier parent and penetrance in the molecular assay is complete, we used classical segregation analysis with parameters for segregation frequency of affected (p) and ascertainment probability (π) assuming no families unable to segregate ($h = y = 0$) or with sporadic cases resulting from parentage error, mutation, or mistyping ($x = 0$) (14). All nuclear families initially were divided into complete selection (no proband offspring) and incomplete selection (with a proband offspring). For carrier mothers, the ascertainment probability π under incomplete selection was estimated from the distribution of probands among affected sibs (14). The 49 families with 2 or more affected sibs gave $\hat{\pi} = .141$ with a residual χ^2 of 0.92 in a sparse table with 6 degrees of freedom.

Carrier fathers (normal transmitting males, or NTMs) are subject to a different bias from carrier mothers, because their sons are not at risk. An NTM without a daughter is unlikely to be ascertained, and the probability of ascertainment through an affected grandson increases with the number of daughters. Even in the absence of affected grandsons, the combination of a father who may be an NTM and one or more daughters who may be obligate carriers is more likely to attract genetic interest than the sons, who must be noncarriers. Therefore, NTMs were analyzed separately in two ways: without allowance for this bias, and under single selection ($\pi \to 0$).

In the analysis of intermediate alleles, such alleles were taken as affected and other alleles, with the exception of pre- and full mutations, which were excluded from the analysis, were treated as normal. Therefore, probands and ancestral probands in this analysis were defined exclusively by an intermediate allele. When a boy with learning difficulties and his mother were both tested in the survey and the mother was a carrier, the pair was included whether or not the retarded son was a carrier, and therefore the mother was taken as the proband. The handful of diagnostic families in which a mother and child carried an intermediate allele were assumed to have single selection. Segregation from heterozygotes for two different common alleles was subject to complete selection, the larger allele being taken as affected.

FRAXE. Unfortunately, we had insufficient families with either a FRAXE full or premutation to undertake a segregation analysis. However, sufficient data were available on families with intermediate and common alleles of FRAXE to permit an analysis of their segregation, which was done in exactly the same way as for FRAXA intermediate alleles and common alleles.

Statistical Analysis. Because we want to test the null hypothesis that the segregation frequency p (allowing for ascertainment) has the Mendelian value of .5, we used classical segregation analysis (14). There are two sampling frames: selection through a parent without regard to genotypes of children (complete selection) and selection through a proband

Table 2. Segregation of FRAXA full- and premutation alleles in offspring of carrier fathers

Selection	Tested offspring, $p = .5$			ML estimate,	All offspring, $p = .5$			ML estimate,	Tested vs. not, χ^2_1
	ML score, U_p	Information, K_{pp}	χ^2_1	p̂	ML score, U_p	Information, K_{pp}	χ^2_1	$\hat{p}$	
Complete	22.0	60.0	8.07	.867	18.0	68.0	4.76	.765	5.31
Incomplete ($\hat{\pi} = .141$)	9.0	56.0	1.45	.659	9.4	80.0	1.11	.617	0.35
Complete + incomplete	31.0	116.0	8.28	.767	27.4	148.0	5.07	.685	3.62
Single all	18.0	92.0	3.52	.696	14.0	124.0	1.58	.613	2.44

Complete vs. incomplete $\chi^2_1 = 1.24$.

Table 3. Segregation of FRAXA intermediate alleles from carrier parents

Selection	Null hypothesis, $p = .5$			ML estimate,	Equivalent meioses	
	ML score, U_p	Information, K_{pp}	χ^2_1	$\hat{p}$	Carrier	Total
Proband mother–retarded child	54	244	11.95	.721	44	61
Complete–other tested children*	16	520	0.49	.531	69	130
Mother carrier	−10	396	0.25	.475	47	99
Father carrier–tested children	26	124	5.45	.710	22	31
Father carrier–all children	14	156	1.26	.590	23	39

Retarded vs. other heterogeneity $\chi^2_1 = 6.03$. Father carrier vs. mother carrier (tested children, not retarded) $\chi^2_1 = 5.21$.
*Includes single selection with proband omitted.

child (incomplete selection). In the first case the relevant likelihood is a function of p only. In the second case, the ascertainment probability π is a nuisance parameter specified by hypothesis or estimated from the distribution of a probands among r affected children within a sibship of size s and/or the distribution of t ascertainments per proband. If the only effect of ascertainment is to disregard sibships with no affected individuals ($r = 0$), the distribution of r is a truncate binomial and families are said to be sampled by *truncate selection* ($\pi = 1$). If π approaches 0, there is rarely more than one proband per sibship; this is *single selection*, sibships are ascertained in proportion to the number affected, and omission of the proband gives a complete distribution among s-1 sibs. The general case is $0 \leq \hat{\pi} \leq 1$, where $\hat{\pi}$ signifies a maximum likelihood estimate. Because the number of times a proband was ascertained is poorly specified, we used probands among affected children. Segregation analysis gives for $p = .5$ a maximum likelihood score U_p and information K_{pp}, which may be converted into equivalent number of meioses $n = K_{pp}/4$ and equivalent number of carrier transmissions $(.5 + U_p/K_{pp})N$. This transformation gives the actual counts for complete and single selection and counts corrected for ascertainment otherwise. Goodness of fit to the null hypothesis that $p = .5$ was tested by $\chi^2_1 = U_p{}^2/K_{pp}$.

RESULTS

Full and Premutations: FRAXA. The analysis of carrier mothers (Table 1) shows close agreement with Mendelian expectation, both for the 48 meioses under complete selection and the 128 equivalent meioses under incomplete selection. In the pooled sample the segregation frequency p is very slightly less than .5, providing no evidence of meiotic drive for full and premutations from carrier mothers.

The data on carrier fathers are more complex. With rare exceptions such normal transmitting males are intellectually normal and carry a premutation. Clinical geneticists are alert to the fact that all daughters but no sons inherit the premutation. Testing is superfluous for sons, and so the effort expended on contacting a family increases with the number of daughters. Because it is not clear *a priori* how to model this, we examined several possibilities (Table 2). Tested offspring from NTMs under complete selection have a significant excess of females ($\chi^2_1 = 8.07$). This is reduced but remains significant when two untested offspring are included, taking all females as affected and all males as normal ($\chi^2_1 = 4.76$). The sample under incomplete selection has a nonsignificant excess of females, which is significant when combined with complete selection ($\chi^2_1 = 8.28$ for tested offspring, $\chi^2_1 = 5.07$ when eight untested offspring are included). However, if ascertainment is proportional to the number of daughters (single selection), the excess of females is suggestive but nonsignificant for tested offspring ($\chi^2_1 = 3.52$) and reduced when eight untested offspring are included ($\chi^2_1 = 1.58$). We believe that this is the appropriate analysis, and the significant results under other assumptions are a result of ascertainment bias. Heterogeneity between tested and untested offspring is not significant, but this must reflect the small number of tested offspring.

Ascertainment of nuclear families with carrier fathers is biased in ways that are difficult to model faithfully. Considering the absence of any well proven case of meiotic drive in man, the evidence in this small sample, which is biased in more than one way, is not sufficiently strong to reject parsimony and infer meiotic drive.

Intermediate Alleles: FRAXA and FRAXE. A carrier of an intermediate allele is *affected* and a noncarrier is *normal*, with only tested individuals being enumerated. A *proband* is a carrier parent ascertained independently of carrier status of children, who may be selected for learning disability. Therefore, these children are sampled under complete selection, whereas the sibship containing the proband is under single selection.

Fathers with FRAXA intermediate alleles show to some degree the bias toward testing daughters noted above for pre- and full mutations. For FRAXA-intermediate mothers (Table 3) there is heterogeneity between transmissions to learning disability children and other transmissions ($\chi^2_1 = 6.03$). The segregation frequency to learning disability children (.721) is clearly above the expected value of .5 ($\chi^2_1 = 11.95$), whereas transmission to other children (who may include those with unrecognized learning disabilities) is unremarkable ($\chi^2_1 = 0.49$). The distribution of haplotypes for nearby markers DXS548, FRAXAC1, and FRAXAC2, notably the 2-1-3 haplotype associated with intermediate alleles for FRAXA, does not differ significantly between transmitted and nontransmitted chromosomes (Table 4). This suggests that our observations are not the result of linkage disequilibrium between a haplotype associated with intermediate alleles and a gene causing learning disability. Thus, our analysis agrees with case-control evidence that intermediate alleles for FRAXA are a risk factor for learning disability (11).

The much smaller number of observations for FRAXE are in surprisingly good agreement (Table 5). Of 12 transmissions from carrier parents to learning-disability children, 9 received the intermediate allele ($\chi^2_1 = 3.00$), consistent with the case-control study where the excess of retardation ($\chi^2_1 = 4.39$) is significant (11). It seems that intermediate alleles for FRAXE are also a risk factor for learning disability, despite the less severe phenotype of FRAXE full mutations compared with FRAXA.

Common Alleles: FRAXA and FRAXE. There is no evidence for segregation distortion in mothers heterozygous for different common alleles at FRAXA (Table 6) or FRAXE (Table 7) as reported by Chakraborty *et al.* (8) for myotonic dystrophy.

Table 4. Haplotypes with the FRAXA intermediate allele in transmitted and nontransmitted chromosomes

Haplotype	Transmitted	Nontransmitted	Total
2-1-3	16	4	20
Other	20	10	30
Total	36	14	50

$\chi^2_1 = 1.06$.

Table 5. Segregation of FRAXE intermediate alleles from carrier parents

Selection	Null hypothesis, $p = .5$			ML estimate,	Equivalent meioses	
	ML score, U_p	Information, K_{pp}	χ^2_1	$\hat{p}$	Carrier	Total
Complete–retarded child	12	48	3.00	.750	9	12
Complete–other tested children*	0	64	0.00	.500	8	16
Mother carrier	−2	12	0.33	.333	1	3
Father carrier–all children	0	64	0.00	.500	8	16

Retarded vs. other heterogeneity $\chi^2_1 = 1.71$.
*Includes single selection with proband omitted.

DISCUSSION

Early studies on FRAXA defined affection as mental impairment and/or chromosome fragility. The segregation frequency p was consistently less than .5, which, as we now know, is because of transmitted premutations (15, 16). Full-mutation carrier females (recognized with some error by mental retardation and/or the fragile X phenotype) were in agreement with $p = .5$, but in this type of material no test of meiotic drive is conclusive.

The observations reported here provide no evidence for segregation distortion among the offspring of females with a pre- or full-FRAXA mutation: we had insufficient material to undertake such an analysis for FRAXE families. Our data are in agreement with those of Sherman *et al.* (17) in an unbiased sample of conceptuses from females with a pre- or full-FRAXA mutation. The small number of transmissions from males with a FRAXA premutation suggested an excess of affected, i.e., an excess of female compared with male offspring. We think that bias toward testing daughters is by far the most reasonable explanation for our results, but until more data under a well defined sampling scheme are available for analysis, segregation distortion cannot rigorously be excluded for transmitting males.

Our observation that there appeared to be an excess of intermediate alleles for both FRAXA and FRAXE among boys with special educational needs by comparison with the maternal chromosome not transmitted to the proband son could formally be explained as (*i*) the result of segregation distortion with the preferential transmission of the intermediate allele, (*ii*) an unexpected biological effect of the intermediate allele for both FRAXA and FRAXE, or (*iii*) linkage disequilibrium between haplotypes, such as 2-1-3 for FRAXA, associated with intermediate alleles and as yet unrecognized genes associated with learning impairment. The analysis reported here excludes segregation distortion as an explanation for the excess of intermediate alleles among learning-disabled sons of carriers and provides no evidence that the association between intermediate alleles and learning disabilities is specific to certain haplotypes. The high significance of this association argues against a type I error.

We attempted to quantify the magnitude of the effect of intermediate alleles for FRAXA on boys with learning difficulties. If the transmission frequency of intermediate alleles to n children with learning disabilities is p, with expectation .5 if there is no allelic association, the relative risk (RR) is $p/(1 - p)$ with variance $p/n\ (1 - p)^3$. We estimate p from retarded sons as .721, and so RR = 2.58 ± 0.74. If the gene frequencies in the general population of males are q, r, and $1 - q - r$ for intermediate and premutations, full mutations, and common alleles, respectively, then the frequency of learning difficulty is $f = r + q\mathrm{RR}c + (1 - q - r)c$, where $c = (f - r)/(q\mathrm{RR} + 1 - q - r)$ is the risk for learning difficulty in males with a common allele, cRR is the penetrance for the intermediate allele, and $c(\mathrm{RR} - 1)$ is the attributable risk. Among males who do not have learning difficulty for other reasons, the attributable penetrance is $c(\mathrm{RR} - 1)/(1 - c)$, corresponding to total penetrance of $c(1) + (1 - c)\ [c(\mathrm{RR} - 1)/(1 - c)] = c\mathrm{RR}$.

In our population the frequency of learning difficulty is defined by the proportion of 5- to 18-year-old boys who meet our criteria for inclusion, or $f = 1{,}502/37{,}028$ (11). Currently, our best estimate of the FRAXA full-mutation frequency is $r = 1/4{,}500$, and of the intermediate allele is $q = 14/723$. Therefore, $c = .039$, and the corresponding risk for the intermediate allele is .101. Whereas the full mutation contributes $r = .0002$ to the frequency of "unexplained" learning difficulty, the intermediate allele contributes $q\mathrm{RR}c = .0020$. Taking cq as constant, the corresponding variance is $(cq)^2\ p/n\ (1 - p)^3$, or a standard error of .0006. The attributable penetrance of intermediate alleles is .064, slightly greater than the attributable risk (.062), which contributes .0012 to the frequency of learning difficulty (Table 8). This excludes the baseline prevalence ($cq = .0008$), which is included in the total prevalence (.0020). Therefore, the intermediate allele, despite its low penetrance, is so much more frequent than the full mutation that it contributes more to learning difficulty, at least as defined in the population under study. It remains to be determined how such "learning difficulty" is expressed and whether the intermediate allele has any effect on boys not classified by schools as having a learning disability. The FRAXE data are as yet too sparse for a similar calculation.

For FRAXA we also made a preliminary estimate of the effect of intermediate alleles on IQ. The standard normal deviate is 1.76 for $Q = .039$ and 1.28 for $Q = .101$, where Q is the area beyond the standard normal deviate. Assuming that the distribution of IQ is adequately approximated by a normal distribution with standard deviation 15, the mean IQ deficit for intermediate alleles in males is $15(1.76 - 1.28) = 7.2$. The deficit for premutation alleles may be greater. It remains to be seen whether these predictions are confirmed in a random sample.

Our evidence against meiotic drive for FRAXA and FRAXE mothers, in whom dynamic mutation from pre- to full mutation occurs, is relevant to other claims of meiotic drive in trinucleotide repeats. One of these was by Chakraborty *et al.* (8), who found excess transmission of the larger CTG repeat

Table 6. Inheritance of FRAXA alleles in the common range from carrier mothers to their sons

Difference between alleles (number of repeats)	Allele transmitted	
	Larger	Smaller
1–5	155	142
6–10	88	107
11–15	25	22
>15	7	10

Table 7. Inheritance of FRAXE alleles in the common range from mothers to their sons

Difference between alleles (number of repeats)	Allele transmitted	
	Larger	Smaller
1–5	200	215
6–10	64	70
11–15	21	17
>15	0	1

Table 8. Effects of FRAXA alleles in males: Parameters and estimates

Allele	Number of repeats	Frequency	Relative risk	Penetrance		Prevalence	
				Total	Attributable	Total	Attributable
Premutation (P) +	41–200	q	$RR = p/(1 - p)$	RRc	$(RR - 1)c/(1 - c)$	$qRRc$	$q(RR - 1)c$
Intermediate (I)		.0194	2.58	.101	.064	.0020	.0012
Full mutation (F)	>200	r	$1/c$	1	1	r	r
		.0002	25.64	1	1	.0002	.0002

from females heterozygous at the myotonic dystrophy (DM) locus. The data were presented in admirable detail, which permitted a further analysis (18). The significance level is modest ($\chi^2_1 = 4.77$, $P < .05$) and is overshadowed by heterogeneity among mating types ($\chi^2_5 = 19.01$, $P < .01$). A Bonferroni correction for the fact that male transmission was also tested makes the evidence nonsignificant, as does an F test against the residual. The observations are unusual but they provide no evidence of meiotic drive. Other claims for trinucleotide repeat alleles are summarized in Table 9. They all involve diseases in which adult males are more likely to come to medical attention than females (19), and none appear to have made any allowance for incomplete ascertainment. Primary and ancestral probands were not identified, and so no rigorous analysis of this material is possible. However, no study gives a significant difference between male and female transmission, the hallmark of meiotic drive. Therefore, we conclude that so far there is no convincing evidence for this phenomenon in trinucleotide repeats.

A few claims of meiotic drive have been made for other diseases. Williams *et al.* (20) typed sperm for segregation of ΔF508 at the cystic fibrosis (CFTR) locus. Data from a sample of 539 sperm typed only for the CFTR locus suggested segregation distortion, the frequency scored positive for the ΔF508 allele being only 44 percent among typed sperm. However, when the segregation frequencies for CFTR and a coamplified unlinked marker were compared in 177 sperm, no differences were detected. Leeflang *et al.* (9) noted that these studies did not take into account PCR errors that affect genotyping of sperm. Munier *et al.* (2) reported an excess of affected from male carriers of retinoblastoma in eight pedigrees. This study was unique in attempting ascertainment correction. Nevertheless, a striking excess of affected remained even when two ancestral probands were removed in addition to clinical probands ($\chi^2 = 6.12$). Heterogeneity between male and female carriers was nonsignificant ($\chi^2 = 2.49$). Similar observations were made on a much larger sample from the literature, where no ascertainment correction was possible. Evans *et al.* (3) reported an excess of affected among children of female carriers for cone-rod retinal dystrophy ($\chi^2 = 5.89$) in a 7-generation pedigree with 277 members. They did not describe ascertainment except that information was obtained from three senior family members and previous pedigree studies. They cautiously concluded that the pedigree suggested meiotic drive. Finally, Jarvik *et al.* (4) noted an excess of affected sons from male carriers of split hand/split foot ($\chi^2_1 = 4.92$), with no information about ascertainment and a curious interaction between sexes of carrier parent and affected children. These observations on diseases not mediated by trinucleotide repeats are heterogeneous and represent a few positive results from a vast literature in which the segregation difference between males and females (when tested) was nonsignificant. In this type of material several biases are possible, including preferential testing of mildly affected relatives. Although we cannot reject meiotic drive as confidently as for trinucleotide repeats, we remain skeptical about these claims.

Evidence suggestive of meiotic drive continues to be reported, most recently for Machado–Joseph disease in Centre d'Étude du Polymorphisme Humain pedigrees (22). Unlike the similar study of myotonic dystrophy (18), the data were not reported in sufficient detail for heterogeneity analysis. Unlike an earlier claim of excess transmission of larger alleles from affected fathers, there was excess transmission of smaller alleles from normal mothers ($p = .016$). The authors noted that "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. . . . Thus, these findings should be replicated in an independent, large set of families," to which we add that they should be subjected to tests for mistyping of similar alleles, especially in intercrosses.

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Table 9. Claims from the literature of meiotic drive in trinucleotide repeat diseases (L = larger, S = smaller allele)

Disease	Definition of L	Paternal carrier		Maternal carrier		χ^2	Reference
		L	S	L	S		
DRPLA*	Affected	54	47	36	50	2.51	10
MJD*	Affected	17	9	26	21	0.70	10
DM	≥19 repeats	74	50	65	53	0.52	5
	Affected	314	211	207	165	1.55	6
	>S	126	116	146	107	1.59	21
Total		585	433	480	396	1.36	

Heterogeneity, $\chi^2_4 = 5.51$.
*Assuming all probands from carrier fathers, no ancestral probands, and all nonindex sibships under complete selection.

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