LETTERS TO THE EDITOR

Meiotic drive at the myotonic dystrophy locus

The mutation underlying myotonic dystrophy (DM, MIM* 160900) is the expansion of a CTG trinucleotide repeat sequence at the 3' untranslated region of a protein kinase gene (MT-PK).¹ The kinetics of this process is influenced by the sex of the transmitting parent and size of the parental allele.²⁻⁴ Congenital DM (CDM) occurs almost always with maternal transmission. Only two patients with CDM have proven paternal inheritance.^{5,6} Maternal transmission is considered to be the result of a large intergenerational increase of the CTG repeat size,⁷ while repeat length contractions are more likely inherited if the mutated allele is of paternal origin.⁸ However, the range of expansions is wider for alleles transmitted by fathers with fewer than 100 repeats (range 41 to 95).⁹ This has suggested a male bias in the generation of new contracted or expanded DM alleles.¹⁰ Carey *et al*¹¹ described an unusual segregation of the MT-PK alleles with a CTG number ≥ 19 in healthy persons heterozygous for repeats in the wild type size range, and suggested the possibility of meiotic drive at the DM locus.

We investigated 251 Italian and Spanish DM pedigrees by clinical and molecular analysis to substantiate differential transmission of the MT-PK alleles. The 210 fathers had CTG repeats in the range of 54 to 1100, while the 178 mothers had expansions in the range of 90 to 2000. Among 897 sibs investigated we found a significant proportion of affected sibs (58.1% *v* 41.9%) ($Z = 4.663$, $p < 0.001$). The 314 DM offspring born from affected fathers had expansions in the range of 100 to 1900, while the 207 DM offspring born to affected mothers had repeats in the range of 70 to 2200. In addition, we observed a striking distortion of segregation with sex. The mutant parental allele was significantly more often transmitted to sons (table). The daughters had received the DM allele in similar proportions from their mother and father (table). Fathers had preferentially transmitted the mutant allele to sibs ($p < 0.001$). The un-

affected sibs had a male to female ratio of 1.020 compared to 1.144 in affected sibs. The average family size was similar in the progeny of affected and unaffected parents (3.5). It is likely that the segregation distortion observed was not the result of a limitation in family size after the birth of an affected child since the average family size of affected fathers was larger than that of affected mothers.

Our results show that DM alleles, unlike the wild type alleles, are transmitted preferentially to sons, and that the sex of the affected parent influences the probability of a child inheriting the disease gene. In fact, more affected sibs are born to affected fathers than to affected mothers. Our data expand the results of Carey *et al*¹¹ and point to distortion in favour of CTG alleles ≥ 19 in male transmission. The present results also support the suggested mechanism of an expansion of the DM gene pool through preferential inheritance of the mutant alleles from male to male.¹⁰ This mechanism could involve cis-acting elements associated with (proto) mutated alleles, affecting gamete viability or fitness, or survival of the zygote. It is noteworthy that inheritance of the cone-rod retinal dystrophy locus, which maps in the DM region (19q13.3-q13.2), is also influenced by meiotic drive.¹²

Although unusual segregation of trinucleotide mutations awaits verification in other diseases, one can speculate that meiotic drive is an evolutionary force which increases the population frequency of dynamic alleles.

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Natural history and postmortem anatomy of a patient with tetra-amelia, ectodermal dysplasia, peculiar face, and developmental retardation (MIM 273390)

We would like to document the follow up details of an infant originally reported by us in 1987¹ with a probable new malformation syndrome. The clinical features of the male proband, at that time 1 year old, included tetra-amelia, hypotrichosis, upward slanting palpebral fissures, lack of lacrimal openings, hypoplastic lacrimal ducts and sacs with exterior openings, prominent bulbous nose, large downturned mouth, high narrow palate, sacral dimple, absence of the inner half of the right clavicle, bilaterally undescended testes, and developmental retardation. The clinical features of the next sib (a therapeutically aborted fetus) closely resembled those of the proband. As the parents were second cousins, we postulated that this malformation syndrome was the result of the homozygous state of a rare autosomal recessive mutation.

Since the parents refused to care for the proband at home, he was admitted into an institution for severely mentally and physically handicapped children. His temperature increased when the ambient temperature was high, and he suffered from persistent constipation. He never developed eyebrows, eyelashes, or hair on his head. Although the findings of his electroencephalogram were within normal limits, a CT scan of the brain showed ventriculomegaly and increased subarachnoid space. At 8 years 5 months of

Transmission of the DM alleles to the progeny

	Paternal DM origin				Maternal DM origin			
	DM	Normal	Total	p	DM	Normal	Total	p
Sons	166	105	271	<0.001 99% confidence limits (115-156)	112	71	183	0.002 99% confidence limits (75-108)
Daughters	148	106	251	0.004 99% confidence limits (106-145)	95	94	189	0.884 99% confidence limits (77-112)
Total	314	211	525	<0.001 99% confidence limits (234-291)	207	165	372	0.026 99% confidence limits (162-210)