Segregation distortion in myotonic dystrophy

Alex C Magee, Anne E Hughes

Abstract

Myotonic dystrophy (DM) is an autosomal dominant disease which, in the typical pedigree, shows a three generation anticipation cascade. This results in infertility and congenital myotonic dystrophy (CDM) with the disappearance of DM in that pedigree. The concept of segregation distortion, where there is preferential transmission of the larger allele at the DM locus, has been put forward to explain partially the maintenance of DM in the population. In a survey of DM in Northern Ireland, 59 pedigrees were ascertained. Sibships where the status of all the members had been identified were examined to determine the transmission of the DM expansion from affected parents to their offspring. Where the transmitting parent was male, 58.3% of the offspring were affected, and in the case of a female transmitting parent, 68.7% were affected. Studies on meiotic drive in DM have shown increased transmission of the larger allele at the DM locus in non-DM heterozygotes for CTGn. This study provides further evidence that the DM expansion tends to be transmitted preferentially.

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Regional Genetics Service, A Floor, Belfast City Hospital Trust, Lisburn Road, Belfast BT9 7AB, Northern Ireland
A C Magee

Department of Medical Genetics, The Queen's University of Belfast, University Road, Belfast BT9 7AB, Northern Ireland
A E Hughes

Correspondence to:
Dr Magee.

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Segregation distortion has been shown to be the basis for altered transmission ratios in genetic conditions expected to follow mendelian inheritance patterns.¹ Myotonic dystrophy (DM) is the commonest adult form of muscular dystrophy with an incidence of around 1/8000.² The loss of reproductive fitness that is observed in the typical three generation anticipation cascade in DM does not correlate with the maintenance of DM in the population. Carey *et al*³ studied segregation of the normal alleles in families with no known history of DM. They found segregation distortion in favour of the larger allele (≥ 19 CTG) in heterozygous normal males and suggested that a process of meiotic drive could be responsible for the maintenance of the larger DM allele in the population, these alleles being capable of expanding to premutation and mutation levels.

Gennarelli *et al*⁴ studied segregation of DM alleles in affected families and found significant segregation distortion in favour of the expanded DM allele with 58.1% of sibs (n=897) affected, and preferential transmission from fathers to sons. Hurst *et al*⁵ reanalysed data from the above studies and agreed that there was selection in favour of the relatively long allele, but did not support the findings of male specific meiotic drive. Shaw *et al*⁶ also looked at transmission of the larger DM allele in normal heterozygous parents and found a higher transmission rate of the larger allele from mothers, with a significant overall finding of segregation distortion. In their study of DM allele segregation in CEPH families, Chakraborty *et al*⁷ avoided the statistical artefact of multiple testing and found evidence of transmission of larger alleles from females.

Segregation distortion has also been reported in dentatorubral-pallidolusian atrophy (DRPLA) and Machado-Joseph disease (MJD),⁸ both of which are associated with CAG trinucleotide repeat expansions, with the drive being more prominent in the male meioses. Linkage of cone-rod retinal dystrophy to chromosome 19q13.1-q13.2 in a large pedigree also showed segregation distortion.⁹

We studied the segregation of the expanded DM allele in Northern Ireland pedigrees and provide further evidence for preferential transmission of the disease associated expansion.

Patients and methods

Fifty-nine DM pedigrees were identified in a recent epidemiological survey of DM in Northern Ireland.¹⁰ Sibships where the ascertainment of affected and unaffected subjects was complete were examined and assessed depending on whether the transmitting parent was male or female and on the sex distribution within the sibship.

Results

Forty-four sibships were ascertained completely with 108 children, of whom 68 (63%) were affected. In 20 sibships the affected parent was male with 60 offspring, 28 sons and 32 daughters. Ten sons and 15 daughters (41.7%) are unaffected. Eighteen sons and 17 daughters (58.3%) have DM. In 24 sibships the affected parent was female with 48 offspring, 23 sons and 25 daughters. Five sons and 10 daughters (31.3%) are unaffected. Eighteen sons and fifteen daughters (68.7%) have DM, as shown in table 1.

If the index case is excluded to compensate for bias of ascertainment, there is no change in the unaffected offspring of the transmitting males. Their affected offspring data are reduced to 13 sons and 12 daughters, thus show-

Table 1 Transmission of the DM alleles to offspring

	Affected parent male (n=20)			Affected parent female (n=25)		
	Daughters	Sons	Total	Daughters	Sons	Total
Normal	15	10	25 (41.7%)	10	5	15 (31.3%)
DM	17	18	35 (58.3%)	15	18	33 (68.7%)
Total	32	28	60 (100%)	25	23	48 (100%)

Table 2 Transmission of the DM alleles to offspring (excluding index cases)

	Affected parent male (n=18)			Affected parent female (n=18)		
	Daughters	Sons	Total	Daughters	Sons	Total
Normal	15	10	25 (50%)	9	5	14 (38.9%)
DM	13	12	25 (50%)	14	8	22 (61.1%)
Total	28	22	50 (100%)	23	13	36 (100%)

ing the expected transmission ratio for classical autosomal dominant inheritance. However, when the index cases are excluded from the data for the female parents, five sons and nine daughters are unaffected, and eight sons and 14 daughters have DM (table 2). Therefore affected female parents show a transmission rate of 61.1% in favour of the DM expansion.

Discussion

We found an overall transmission of the DM expansion of 63% (statistically significant $p=0.007$, $\chi^2=7.26$, $df=1$). This preferential transmission of the DM expansion supports the findings of previous studies.¹¹⁻¹³ Two of these^{11,12} were undertaken before the recognition of the congenital form of myotonic dystrophy,¹⁴ so the transmission figures in these papers could be expected to be an underestimate. Klein¹² commented that the transmitting parent was male in 50.5% of cases, female in 32.4% (this lower figure probably because the study was before the recognition of CDM), and unknown in 17%. The study of Gennarelli *et al*⁸ found 58.1% of offspring to have inherited the DM expansion with preferential transmission from the male, in contrast to our observations. An additional recent report,⁶ studied transmission of DM alleles within the normal range and noted preferential transmission of the larger allele in females but not in males.

In our study, when sex of the transmitting parent is taken into account, females transmitted the DM expansion to 68.7% ($p=0.009$, $\chi^2=6.75$, $df=1$) of their children. Excluding the index case considerably diminishes the statistical significance ($p=0.18$, $\chi^2=1.78$, $df=1$). This may be partially accounted for by a restriction in family size after the birth of an affected child. The average family sizes for affected fathers and mothers in the Northern Ireland study are 3.9 and 2.9 children, respectively. When mothers of CDM sibships are taken as a separate group, the average family size decreases to 2.3. Also, when the index case is taken into consid-

eration, families with a single affected child are automatically excluded.

It is interesting to look at cone-rod retinal dystrophy which also shows increased transmission (63%) from affected mothers to their offspring.⁹ Cone-rod retinal dystrophy is linked to 19q13.1-13.2, just upstream from the DM region. If, as we suspect, segregation distortion does exist, the questions remain as to whether it is the result of factors at the DM locus or the effects of other linked genes or gene interactions. Increased female recombination in the DM region would suggest that distortion is not the result of closely linked genes alone.

The debate as to whether or not segregation distortion exists in DM is further fuelled by our findings. This, coupled with the high prevalence of a premutation allele (CTG>20) in the population, may explain why the rapidly progressive phenotype owing to anticipation has not eradicated this disorder from the gene pool.

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