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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Keywords: myotonic dystrophy; segregation distortion

Segregation distortion has been shown to be the basis for altered transmission ratios in genetic conditions expected to follow mendelian inheritance patterns. Myotonic dystrophy (DM) is the commonest adult form of muscular dystrophy with an incidence of around 1/8000. 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. 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.

Patients and methods
Fifty-nine DM pedigrees were identified in a recent epidemiological survey of DM in Northern Ireland. 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 40 offspring, 23 sons and 23 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>
<thead>
<tr>
<th>Affected parent male (n=20)</th>
<th>Affected parent female (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daughters</td>
<td>Sons</td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
</tr>
<tr>
<td>DM</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
</tr>
</tbody>
</table>
Table 2  Transmission of the DM alleles to offspring (excluding index cases)

<table>
<thead>
<tr>
<th>Affected parent male (n=18)</th>
<th>Affected parent female (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daughters</td>
<td>Sons</td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
</tr>
<tr>
<td>DM</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
</tr>
</tbody>
</table>

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.\(^1\)\(^-\)\(^13\) 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. Klein\(^15\) 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.\(^16\) 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,\(^9\) 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-

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.

We would like to thank all the families who took part in this study. Ethical approval was granted by the Ethics Committee, Belfast City Hospital Trust.

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