LETTERS TO THE EDITOR

Estimate of germinal mosaicism in Duchenne muscular dystrophy

Germainal mosaicism has been proposed to explain the recurrence of Duchenne muscular dystrophy (DMD) in some families.1-3 In a recent study of 288 Duchenne and Becker (BMD) muscular dystrophy families published in this Journal, Bakker et al4 detected six cases of apparent multiple transmission of 'new' mutations out of 42 studied, indicating that this phenomenon is relatively frequent. According to the authors the most plausible explanation for such multiple transmission, taking into account the absence of mutation in the lymphocytes of the mother or the grandparents, is somatic mosaicism. Based on the above empirical data, they estimated a recurrence risk of approximately 7% (14% if the at risk X haplotype is known) when counselling sisters and mothers of an apparently new DMD mutant. This observation, if confirmed in other studies, has important implications for genetic risk estimates of females at risk belonging to families in which X linked inheritance cannot be proved.

During the last 21 years we have studied in our centre a large sample of families with patients diagnosed as having DMD, which allowed us to test the hypothesis of germinal mosaicism through two simple approaches, summarised below.

(1) We compared the proportion of females with increased serum creatine kinase (CK) among obligate carriers (OC) and probable carriers (PC). A mother was classified as OC when she had at least one son with DMD and one or more affected male relatives through the maternal line (brother or maternal uncle) and as PC when she had two or more DMD sons (or one affected son and one carrier daughter) but with no other affected relatives in previous generations. If the hypothesis of Bakker et al4 is correct there should be a greater frequency of females with raised serum CK among OC than among PC, since those who carry germinal mosaicism in the second group are expected to have normal serum enzymes.

(2) We estimated the proportion of mothers in our sample of PC who might carry germinal mosaicism, based on the proportion of women with raised serum CK among OC. The sample studied in our centre included 549 mothers of DMD patients: 334 mothers of isolated cases, 96 OC, and 119 PC.

For the first analysis only OC and PC were considered. A total of 334 mothers of DMD patients (216 from our centre and 119 from other reported studies) was analysed: 162 were OC and 172 were PC. As seen in table 1, when samples from different studies were pooled, the percentage of women with raised serum CK in the group of OC (64-2%) was significantly greater (p<0.05) than in the group of PC (52-3%).

For the second analysis only our sample was considered. Taking into account that 58-3% among our OC have raised serum CK and that 61 women in our group of 119 PC have increased enzymes, the corrected estimated proportion of OC among PC is 61/0.583 = 105, which corresponds roughly to 88% (105/119) of OC in our sample and consequently about 12% of potential cases of germinal mosaicism.

An interesting observation is that the difference of approximately 12% from our two analyses is very close to the estimated 14% of germinal mosaicism of Bakker et al4 based on empirical data.

Considering approximately 12% of germinal mosaicism and taking into account our sample of 549 DMD families (table 2) we estimated that mothers of DMD patients are distributed in the following proportions: obligate heterozygotes ~62-3%, mothers of sporadic cases ~31%, and carriers of germinal mosaicism ~6-7%.

These figures indicate that in about 69% of the cases there is a considerable risk for further pregnancies. This frequency is still an underestimate since the proportion of autosomal recessive 'Duchenne-like' dystrophy among mothers with normal enzymes is not negligible.12 13

Therefore, although such estimates should be confirmed in other studies, we agree that the probability of germinal mosaicism should be taken into account in calculation of heterozygosity.

Table 1 Proportion of mothers of DMD patients with increased serum CK among obligate carriers (OC) and probable carriers (PC) from different studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>I</th>
<th>% (I)</th>
<th>N</th>
<th>I</th>
<th>% (I)</th>
</tr>
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<tbody>
<tr>
<td>OC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>5</td>
<td>71.4</td>
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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>50.0</td>
<td>6</td>
<td>3</td>
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<td>7</td>
<td>3</td>
<td>9</td>
<td>75.0</td>
<td>6</td>
<td>3</td>
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<tr>
<td>8</td>
<td>8</td>
<td>16</td>
<td>66.6</td>
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<tr>
<td>9</td>
<td>0</td>
<td>1</td>
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<td>2</td>
<td>3</td>
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<td>10</td>
<td>1</td>
<td>11</td>
<td>91.7</td>
<td>2</td>
<td>6</td>
<td>75.0</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>5</td>
<td>62.5</td>
<td>1</td>
<td>2</td>
<td>66.6</td>
</tr>
<tr>
<td>Present study</td>
<td>40</td>
<td>56</td>
<td>58.3</td>
<td>58</td>
<td>61</td>
<td>51.26</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>104</td>
<td>64.2</td>
<td>82</td>
<td>90</td>
<td>52.3</td>
</tr>
</tbody>
</table>

Table 2 Estimated frequency of inherited, sporadic, and 'germinal mosaicism' cases based on serum CK from 549 mothers of DMD patients.

<table>
<thead>
<tr>
<th>Category</th>
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<th>Proportion with raised serum CK</th>
<th>Corrected estimate</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>OC</td>
<td>NC</td>
</tr>
<tr>
<td>Obligate carriers</td>
<td>96</td>
<td>56 (58.3%)</td>
<td>105 (61.0-58)</td>
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<tr>
<td>Probable carriers</td>
<td>119</td>
<td>61 (51.3%)</td>
<td>72 (82.0-58)</td>
</tr>
<tr>
<td>Mothers of isolated cases</td>
<td>334</td>
<td>82 (24.5%)</td>
<td>170 (82.0-58)</td>
</tr>
<tr>
<td>Total</td>
<td>549</td>
<td>199</td>
<td>342</td>
</tr>
</tbody>
</table>

OC=obligate carriers; NC=non-carrier; GM=germinal mosaicism.
risks for females belonging to families with Duchenne muscular dystrophy.

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Identification of a balanced translocation carrier by spouse’s low maternal serum α fetoprotein associated with an aneuploid fetus

There have been numerous reports of fetuses with Down’s syndrome (trisomy 21), trisomy 18, and trisomy 13 having been identified through a low maternal serum α fetoprotein (MSAFP) level. Recently, Winston et al1 reported a fetus with Turner’s syndrome whose mother had a low MSAFP value of 0.34 multiples of the median (MOM) at 16 weeks’ gestation. Since that case report, Drugan et al2 have suggested that genetic counselling for low MSAFP levels should include all chromosome anomalies, not just Down’s syndrome. In their experience, women with low MSAFP values have carried fetuses with partial trisomy of chromosome 22, triploidy, duplication of chromosome 5, and sex chromosome abnormalities, in addition to trisomy 21 and 18. We report here the identification of a paternal balanced translocation owing to his wife’s low MSAFP value, associated with an aneuploid fetus.

A 29 year old woman (G3P0A1 TAb1) presented for genetic counselling owing to a low MSAFP level of 0.19 MOM at 15 weeks’ gestation. Correcting for weight, the MSAFP value was 0.22 MOM. The patient was not diabetic. The only significant pregnancy history was that eight months before this pregnancy, the woman had had a spontaneous abortion at six weeks’ gestation. Her family history was unremarkable. Her husband’s family history was significant for his mother having had a spontaneous abortion at six months’ gestation. He had only one sib and his mother was an only child. His father’s only sib died in an accident.

The couple elected to have an elevated II ultrasound scan followed by a genetic amniocentesis. Ultrasound scan was normal with size equal to dates. Fourteen days after amniocentesis, the fetal karyotype showed extra material on chromosome 4. The couple was contacted and their blood karyotypes were performed.

The results of the couple’s karyotypes showed the husband to have a balanced reciprocal translocation between chromosomes 4 and 18: 46,XY, t(4;18)(q15.2;q11.2). The woman had a normal female karyotype, 46,XX.

We were thus able to identify the abnormal fetal chromosome 4 as being derived from the father’s translocation. The fetus had partial duplication of 18q and partial deletion of 4p: 46,XY, −4,+ der(4)t(4;18)(p15.2;q11.2). The couple elected to terminate the pregnancy. However, fetal death occurred one day before the scheduled procedure.

While the use of the MSAFP screening test is still considered investigational for screening for fetal chromosome abnormalities, we feel that it enabled us to identify a balanced reciprocal translocation carrier parent owing to the unbalanced chromosomal complement in the fetus. Based on pregnancy and family history, there was no indication for genetic counselling or amniocentesis in this couple. Without the indication of the low MSAFP, prenatal diagnosis would not have been offered. While the tissue from the fetus could have been studied, this is not always done nor is it always successful. This couple could have gone through another miscarriage, or had a severely affected child without having the option to prepare.

Although MSAFP screening is not able to detect parental translocations directly, data from this case show the occasional ability to detect a balanced translocation in a parent associated with a low MSAFP and an unbalanced fetal chromosome complement.

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