LETTER TO THE EDITOR

Reproductive fitness and frequency of new mutations in Becker muscular dystrophy: implications for genetic risk estimates

The severe Duchenne muscular dystrophy (DMD) and the more benign Becker muscular dystrophy (BMD) are allelic conditions caused by an abnormal gene located in the short arm of the X chromosome at Xp21.1,2 The incidence of DMD is around 1 in 3000 to 4000 male births and its estimated mutation rate (approximately 1 in 10 000 genes per generation) is the highest for any genetic disease observed in man.3 Becker muscular dystrophy is approximately 10 times less frequent than DMD.4 According to Haldane,5 the mutation rate for any X linked disorder depends on the fertility (f) of affected males, which has important implications for genetic risk estimates. Under such an assumption, for DMD and several other lethal X linked disorders where f=0, 1/3 of the cases will arise from new mutations and the remaining 2/3 will be inherited from carrier mothers.

In X linked conditions in which the fitness is greater than 0, the relative frequency of cases resulting from new mutations decreases. For example, for BMD and haemophilia f=approximately 0.7; consequently the estimated proportion of inherited cases for these two diseases is 9/10 and only 1/10 arises from new mutations.6 However, the differential clinical diagnosis between X linked BMD and the autosomal recessive form of limb-girdle muscular dystrophy (LGMD) among isolated male patients may be extremely difficult and may lead to erroneous estimates of reproductive performance. Therefore, we analysed the reproductive fitness in a sample of patients affected with BMD as compared with LGMD, but including only cases with a positive family history of X linked or autosomal recessive inheritance. The reproductive fitness was estimated for both conditions by determining the number of offspring of affected patients as compared with their unaffected relatives of the same sex and comparable age.

The results, summarised in the table, are surprising since among BMD patients the reproductive fitness was estimated as only 0.12, which is significantly lower than previously reported data (f=0.67). On the other hand, in families with LGMD the fitness of affected males (0.98) was almost normal and significantly greater (Z=8.7, p<0.0001) than that found for BMD and affected LGMD females (0.45; Z=6.13, p<0.0001).

One possible hypothesis to explain the difference between these results and previously published data on reproductive performance in BMD would be that affected patients now have fewer descendants as a result of genetic counselling. However, in our experience, knowing that no affected child will be born in the first generation does not deter the majority of our cases from procreating.

An alternative explanation would be that many isolated male patients diagnosed as having BMD might have the AR form of LGMD or spinal muscular atrophy.7,8 In fact, if male patients (BMD and LGMD) from the present sample were assembled in one single group, considering the oldest proband from each family (No of BMD=19, No of LGMD=11), their estimated reproductive fitness would be 0.48 (although there are almost twice as many BMD as LGMD probands), which is closer to 0.67.

Our observation, if confirmed in other studies, has important implications for genetic risk calculations (using Bayesian calculation) for mothers and sisters of isolated DMD or BMD patients. In addition, if the present estimate for BMD is used in Haldane's formula, it derives that approximately 29% of Becker patients also arise from new mutations. Such figures are very close to the ones recently estimated for X linked DMD.9,10 This is consistent with the finding of a single gene responsible for the severe and more benign forms of X linked muscular dystrophies, suggesting that DMD and BMD are a single entity in which the spectrum of clinical variability is produced by different mutations in the gene. Mutations producing a very benign phenotype have been reported10 and they are not necessarily associated with the muscular dystrophy phenotype,11 which suggests that mutations not altering the phenotype might possibly be missed. We conclude, therefore, that it is difficult to estimate accurately the mutation rate at this locus and that it is important to re-evaluate reproductive fitness in Becker patients from other countries in which the diagnosis is confirmed through X linked inheritance, DNA studies, or dystrophin assessment.

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<th>Disease</th>
<th>Patients</th>
<th>Normal sibs</th>
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<tr>
<td></td>
<td>Sex N</td>
<td>Age (mean, SD) No of offspring</td>
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<tr>
<td>BMD</td>
<td>M 32</td>
<td>29.6 (8.5) 6</td>
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<td></td>
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<tr>
<td>LGMD</td>
<td>M 11</td>
<td>32.9 (11.7) 19</td>
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<td></td>
<td>F 19</td>
<td>31.5 (7.6) 17</td>
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10 Forrest SM, Cross GS, Speer A, Gardner-Medwin D, Burn J, Davies KE. Preferential deletion of exons in Duchenne and Becker muscular dys-

BOOK REVIEWS


It is two years since the last edition of this constantly used classic appeared and while tables in the introduction show us the growth in human genes mapped and identified, the weight of the present volume, with 400 extra pages, is even more tangible evidence. The year 1990 represents a landmark for MIM since its on line counterpart OMIM has now been integrated with the new Genome Database (GBD), allowing both clinical and gene mapping data to be accessed together.

Meanwhile, this hard copy edition contains an abundance of summary tables and chromosome maps relating disease data to gene location and function.

MIM continues to be remarkably successful in trapping new information, a tribute both to the stamina of Dr McKusick and the skills of his helpers; there are two new ones who appear by name for the first time. However, this steady accretion of new material means that the sheer volume of text on some loci is becoming rather indigestible. An important task for the next edition would be a vigorous pruning of outdated material. This will be more difficult than adding new data, but if done critically and systematically should add greatly to the use of the book. It might even result in the next edition shrinking in size! Meanwhile, regardless of the computerised on line version, MIM itself remains an essential companion for everyone in medical genetics; we can only wish Dr McKusick continuing health and energy so that we can look forward to a 10th edition in 1992.

PETER S HARPER


Psychiatric genetics is becoming increasingly popular. The importance of genetic factors in the etiology of many psychiatric disorders has been known for some time. Recent interest has to a large extent been motivated by the enticing possibility of being able to apply modern molecular genetic techniques to the study of mental illness. This book reflects these trends by reviewing the state of current knowledge concerning the genetics of effective disorder, one of the most common forms of psychiatric illness.

It starts with a long chapter discussing diagnostic and methodological issues. Recent years have seen the development of a fairly sophisticated research methodology aimed at the reliable diagnosis and the collection of psychiatric data in a systematic fashion. These methods are described in some detail and anybody contemplating entering this field for the first time will learn much from this chapter, though they may decide to avoid psychiatric genetics altogether when they realise "the wide range of phenomenonologic variabilities among disorders that share disturbance of mood as a primary component of the clinical picture". As the authors acknowledge, both aetiological heterogeneity and pleiotropy probably play a role in producing such a complex picture of overlapping clinical syndromes.

There then follow chapters on each of the traditional methods of psychiatric genetic research; family studies, twin studies, and adoption studies. Research in each of these modalities supports a significant role for genetic factors in the aetiology of mood disorders. This seems to be greater for bipolar disorder (where the patient experiences both manic and depressive episodes) than for unipolar disorder (where the patient experiences only depressive episodes), though the genetic relationship between unipolar and bipolar disorders is still poorly understood. It also seems clear that minor mood disorders and depressive personality characteristics have less of a genetic component than do the major mood disorders.

This is followed by a chapter on quantitative models of genetic transmission. Mathematical modelling studies do not consistently support a specific mode of genetic transmission. Such studies are, however, bedevilled by problems and the authors conclude: "If mood disorders are genetically heterogeneous then the results of modelling studies are meaningless". 