Cosegregation of schizophrenia with Becker muscular dystrophy: susceptibility locus for schizophrenia at Xp21 or an effect of the dystrophin gene in the brain?

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Abstract

A family is reported in which four of five adult patients with Becker muscular dystrophy (BMD) also have schizophrenia or related spectrum disorders. Although the estimated lod scores are not sufficient to conclude the existence of linkage between BMD and schizophrenia, it is suggested that there may be an association between these two disorders. Two alternative hypotheses are proposed to explain such an association: (1) the existence of a susceptibility locus for schizophrenia and spectrum disorders on the short arm of the X chromosome at Xp21; (2) that these psychiatric disorders may result from an abnormality in the expression of the dystrophin gene in the brain.

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A genetic component for schizophrenia is widely accepted, but its mode of inheritance remains unclear. Linkage studies of psychiatric conditions with polymorphic genetic markers have provided contradictory results to date. Autosomal dominant inheritance with reduced penetrance has been suggested as a possible mode of inheritance for schizophrenia. Evidence for a susceptibility locus on chromosome 5 in the region q13-15 in Icelandic and English pedigrees has been reported, but was not supported by studies of other pedigrees. Genetic heterogeneity may explain such disparate findings, but recent reanalysis with new polymorphic markers in that region suggest that it was a false positive result.

The possible association of schizophrenia with other genetic disorders has been discussed previously, but little is known about the occurrence of psychiatric disorders associated with the X linked recessive conditions Becker and Duchenne muscular dystrophy (BMD and DMD). Both are disorders characterised by a progressive muscular degeneration and weakness. They are caused by the absence (DMD), or by abnormalities in quantity or quality (BMD), of the muscle protein dystrophin, encoded by a gene located at Xp21. DMD is a more severe condition, causing death in the second or, more rarely, in the third decade, whereas most patients with BMD can survive to middle age.

Up to 50% of DMD patients have some degree of mental retardation, from severe handicap to borderline, and a reduction of verbal IQ is occasionally found in some cases of BMD. Here, we report a family in which several patients who have BMD also have schizophrenia and schizophrenia spectrum disorder (SSD).

Subjects and methods

The family (figure) was ascertained through a male with Becker muscular dystrophy who had a schizophrenia-like illness. Relatives were...
traced and clinical and psychiatric examinations performed. The diagnosis of BMD was based on X-linked inheritance, disease progression, grossly raised serum creatine kinase (CK) and pyruvate kinase (PK) activities, DNA studies, muscle histology, and dystrophin assay (immunohistochemistry and western blotting). Since serum CK and PK are already raised in preclinical stages of BMD, these enzymes were assessed in all males at risk for BMD. The methods for serum enzyme determinations, DNA, and dystrophin analysis have been described previously.

All psychiatric evaluations were performed during direct interviews with family members using the Schedule for Affective Disorders and Schizophrenia – Life-time version (SADS-L) supplemented by the Structured Interview for DSM-III Personality (SIDP) when necessary. Only subjects older than 20 years were psychiatrically assessed, with the exception of two young BMD boys evaluated through a structured clinical interview by an experienced child psychiatrist. The diagnosis of subjects already dead was made using the Family Informant Schedule and Criteria (FISC), and by the criteria proposed by Kendler et al for the retrospective evaluation of possible SSD. All the psychiatric diagnoses were made according to the Research Diagnostic Criteria (RDC).

Results

The pedigree is depicted in the figure. The majority of members currently live in Brazil, but their progenitors came from Italy on the paternal side and Portugal on the maternal side. The proband (III-21), first ascertained in 1975 at the age of 23, was diagnosed as having BMD and schizophrenia. His grandfather, I-4, had BMD with a very mild clinical progression. He was confined to a wheelchair at the age of 64 and died at the age of 75 of pulmonary oedema. He was a wine producer and a heavy drinker, with a probable diagnosis of alcoholism. He had no other mental or psychiatric disorder. He had one unaffected son (II-3) and six BMD carrier daughters, who between them had a total of eight daughters and 11 sons, seven affected with BMD. In addition, four family members (II-8, III-14, III-19, and II-21) had lepromy. The diagnosis of BMD could be excluded in other at-risk males from generation III and IV on the basis of normal serum CK and PK activities.

DNA analysis in Becker patients showed an ‘in-frame’ deletion in the region encompassed by exons 45 to 49, and the presence of an RFLP of exon 51 detected with probe C56a and restriction enzyme PstI. Chromosome analysis showed no abnormality. Among four females from generation III who agreed to collaborate, III-11 and III-27 were identified as BMD carriers and III-12 and III-28 as non-carriers, based on the presence (III-11 and III-27) or absence (III-12 and III-28) of the RFLP of exon 51 detected in affected patients. Dystrophin western blot analysis showed a protein of reduced molecular weight (390 kDa upper band) compatible with the DNA deletion. Immunohistochemical analysis showed a pattern typical of BMD.

Psychiatric diagnoses in the five BMD patients who reached adulthood and other members of the family are listed in Table 1. Two boys (III-29 aged 10, and III-30 aged 4) are below the age risk for schizophrenia, but patient III-29 has an attention deficit and hyperactivity disorder. With the exception of a single episode of major depression in subject III-1, the unaffected males in generation III are all psychiatrically normal.

Among other family members, only one BMD carrier (III-11) has a paranoid personality which could be included in a broad concept of schizophrenia spectrum disorder. However, this is a complex case with other psychiatric diagnoses (Briquet’s disease and obsessive-compulsive disorder) and bitemporal epilepsy, which is itself associated with a higher prevalence of psychiatric disorders.

LINKAGE ANALYSIS

Two point analysis between the BMD gene and schizophrenia spectrum disorder (SSD) was performed using the computer program LINKAGE and considering different penetrance values (K) for the assumed SSD genotype (Table 2). The two young BMD patients, III-29 and III-30, were not taken into account. The maximum lod score (1.49) was obtained at \( \theta = 0 \) and \( K = 0.7 \). If III-29 is considered as affected the maximum lod score would increase to 1.85 at \( \theta = 0 \) and \( K = 0.7 \).

Discussion

The transmission of schizophrenia spectrum disorder (SSD) in this family is compatible with an X-linked recessive pattern of inheritance. The estimated lod scores are not sufficient to prove the existence of linkage between BMD and schizophrenia. However, the observation that five adult male BMD patients in the pedigree four have schizophrenia or SSD, while six unaffected males have no psychiatric condition, warrants further examination.

X-linked inheritance for psychiatric disorders has been proposed, in particular, a predisposing locus for manic-depression at Xq28. The suggestion that there might be a locus predisposing to schizophrenia on the X chromosome is based on the following. (1) There is a body of opinion which states that psychotic illness is a continuum from manic-depression through schizoaffective psychosis to schizophrenia with increasing severity of defect state. (2) Schizophrenia-like psychoses are seen more frequently than would be expected by chance among subjects with sex chromosome aberrations. (3) Schizophrenia-like symptoms have been reported in association with Alport syndrome (hereditary nephritis) and fragile X. (4) The finding that there is an excess of same sex over opposite sex pairs in sibs both affected with the disorder. This has led to the pseudoautosomal locus hypothesis for the transmission of psychoses. This
Table 1 Psychiatric and non-psychiatric diagnoses for members of the pedigree.

<table>
<thead>
<tr>
<th>Family members</th>
<th>Psychiatric diagnoses</th>
<th>Non-psychiatric diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 4</td>
<td>Alcoholism</td>
<td>BMD, very mild progression</td>
</tr>
<tr>
<td>II 1</td>
<td>Recurrent major depression + Alzheimer’s disease</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>II 5</td>
<td>Major depression (SE)</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>II 7</td>
<td>Recurrent major depression + obsessive-compulsive disorder</td>
<td>Leprosy</td>
</tr>
<tr>
<td>II 9</td>
<td>Alcoholism</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>II 10</td>
<td>Alcoholism</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>II 11</td>
<td>Major depression (SE)</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>II 12</td>
<td>Alcoholism</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>III 24</td>
<td>Major depression (SE)</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>III 27</td>
<td>Minor depression</td>
<td>BMD carrier</td>
</tr>
<tr>
<td>III 28</td>
<td>Chronic schizophrenia</td>
<td>BMD, age 10</td>
</tr>
<tr>
<td>III 29</td>
<td>Attention deficit + hyperactivity disorders</td>
<td>BMD, age 4</td>
</tr>
<tr>
<td>III 30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SE = single episode.

Thus, the high genetic loading might allow the segregation of a predisposing mutation at or near the BMD gene. A mixed mode of inheritance has already been postulated for major affective disorders,40 with a major gene producing its effects against a polygenic background.

(2) In this family schizophrenia and related disorders are caused by the effect of an abnormal dystrophin gene in the brain. This may be more common than reported, as it would rarely be identified in the severe forms of DMD since most patients die before the risk period. In fact, such a diagnosis has recently been established by us in the rare case of a DMD patient (with an ‘out of frame’ deletion of exons 47 to 52) who survived to 23 years old (unpublished data). The association of schizophrenia and DMD has also been suggested by other investigators.41 In a recent study of 35 BMD patients,42,43 two had a diagnosis of schizophrenia and one of attention deficit disorder. These patients, as well as the ones from the present family, all have ‘in frame’ deletions in the dystrophin gene. Although the samples are small, these proportions suggest a higher prevalence of schizophrenia as compared with the 1% lifetime risk in the general population.44

A known characteristic of schizophrenia is decreased reproduction by affected subjects.45 Interestingly, this was also observed by us for BMD in a recent study in which we analysed the reproductive fitness in males affected by autosomal recessive limb-girdle muscular dystrophy (LGMD) as compared with X linked BMD.46-47 While in LGMD the fitness was almost normal (f = 0.98), in BMD it was greatly reduced (f = 0.12). Since the physical disability is similar in the two conditions this would not account for the observed differences in reproductive performance. One possibility is that the reduced fitness in BMD could be because of psychological problems in relating to the opposite sex, similar to those observed in schizophrenia.

An isoform of dystrophin, the DMD/BMD product, has been found in the mouse brain,48,49 and its relation to intellectual function is currently under investigation.50 Results from such studies may provide important data for supporting our second hypothesis.

In conclusion, the apparent cosegregation in this family between Becker muscular dystrophy and schizophrenia, if true, could either be the result of a gene contributing to the mental disorder, linked to the BMD/DMD locus, or alternatively a mutation in the dystrophin gene resulting in a direct effect on the brain.

Table 2 Two point lod scores between Becker muscular dystrophy and schizophrenia and schizophrenia spectrum disorders (SSD). Schizophrenia and SSD was treated as a dominant disease with different penetrance values (K).

<table>
<thead>
<tr>
<th>Recombination fraction (θ)</th>
<th>0.00</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
<th>0.20</th>
<th>0.25</th>
<th>0.30</th>
<th>0.35</th>
<th>0.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>1.29</td>
<td>1.19</td>
<td>1.08</td>
<td>0.96</td>
<td>0.83</td>
<td>0.70</td>
<td>0.57</td>
<td>0.42</td>
<td>0.27</td>
</tr>
<tr>
<td>0.5</td>
<td>1.41</td>
<td>1.30</td>
<td>1.18</td>
<td>1.05</td>
<td>0.92</td>
<td>0.78</td>
<td>0.63</td>
<td>0.47</td>
<td>0.30</td>
</tr>
<tr>
<td>0.7</td>
<td>1.40</td>
<td>1.38</td>
<td>1.27</td>
<td>1.14</td>
<td>1.00</td>
<td>0.85</td>
<td>0.69</td>
<td>0.52</td>
<td>0.33</td>
</tr>
<tr>
<td>0.9</td>
<td>1.35</td>
<td>1.34</td>
<td>1.28</td>
<td>1.19</td>
<td>1.07</td>
<td>0.92</td>
<td>0.75</td>
<td>0.57</td>
<td>0.37</td>
</tr>
<tr>
<td>1.0</td>
<td>1.48</td>
<td>1.39</td>
<td>1.29</td>
<td>1.21</td>
<td>1.06</td>
<td>0.94</td>
<td>0.78</td>
<td>0.59</td>
<td>0.39</td>
</tr>
</tbody>
</table>

* K = penetrance values.

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