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Does the X-Chromosome Carry the Gene Responsible for Bipolar Disorder? An Offspring with Bipolar Disorder and Coexisting Muscular Dystrophy from a Mother with Bipolar Disorder

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ÖZET:

X-kromozomu bipolar bozukluktan sorumlu geni taşıyor mu? Bipolar bozukluğu olan bir annenin bipolar bozukluğu ve müsküler distrofisi olan oğlu

Bipolar bozukluk aile, ikiz ve evlat edinme çalışmaları göre, güçlü bir genetik yapı göstermekte olup, bipolar bozukluktan sorumlu olan genler belirsizliğini korumaktadır. Bu iletim şekli zayıf karakterize edilmiş iken, genetik çalışmalar X kromozomunun bipolar bozukluktan sorumlu olabileceğini düşündürmektedir. Müsküler distrofi, X-kromozomuna bağlı resesif geçişli bir hastalıktır. Bu vakada, bipolar bozukluğu olan bir annenin çocuğu olan ve bipolar bozukluğa eşlik eden müsküler distrofisi bulunan 35 yaşındaki bir erkek hasta sunuldu. Bu olgu bize, müsküler distrofi ve bipolar bozukluktan sorumlu genlerin X-kromozomu içinde birbirine yakın olabileceği olasılığının dikkate alınması gerektiğini göstermektedir.

Anahtar sözcükler: Bipolar bozukluk, X kromozomu, müsküler distrofi

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ABSTRACT:

Does the X-chromosome carry the gene responsible for bipolar disorder? An offspring with bipolar disorder and coexisting muscular dystrophy from a mother with bipolar disorder

According to family, twin and adoption studies, which consistently indicate a strong genetic component, the specific genes that are responsible for bipolar disorder remain unclear. While the mode of transmission is poorly characterized, genetic studies suggest that the X-chromosome may be responsible for bipolar disorder. Muscular dystrophy is an X-chromosome linked recessively inherited disorder. In this case, we present a 35 year-old male with bipolar disorder and coexisting muscular dystrophy whose mother has bipolar disorder. This case prompts us to consider the possibility that those genes responsible for muscular dystrophy and bipolar disorder might be in close proximity within the same chromosome, namely the X-chromosome.

Key words: Bipolar disease, X chromosome, muscular dystrophy

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INTRODUCTION

Genetic transmission of bipolar disorder (BD) has been known for a long time, but its genetic pathogenesis has not been well established yet (1). Studies in twins have detected higher rates of concordance in monozygotic twins as compared to dizygotic twins (2). Recently, studies have been conducted in many chromosome and gene regions (2p, 4p, 4q, 6q, 8q, 11p, 12q, 13q, 16p, 16q, 18p, 18q, 21q, 22q and the X chromosome) to investigate the relationship with BD. Also, the role of various genes including COMT, DAT, HTR4, DRD4, DRD2, HTR2A, 5-HTT, DISC1, P2RX7, MAOA and BDNF in BD has also been investigated (3). The X chromosome is one of the chromosomes that is emphasized in terms of a relationship with BD. McInnis et al. (1999) performed linkage analysis on Xp22.1 in 153 families and determined that there was a significant relationship between Xp22.1 and BD (4). In other

studies, Ekholm et al. (2002) suggested that the Xq24–q27.1 regions might have a relationship with BD, whereas Zandi et al. (2003) showed that the Xp11.3 region showed a possible relationship with BD (5,6). Based on the previous hypothesis that gamma amino butyric acid (GABA) system disorder leads to BD, the relationship of GABA receptor (GABRA3) gene polymorphism, which is coded by the Xq28 region, with BD has been investigated and the 1-1 genotype was found to be higher in the patients as compared to the controls (7). Moreover, MAOA gene polymorphism, which is another gene coded on the X chromosome, has also been investigated and found to have a significant relationship with BD (8). In conclusion, studies on X chromosome genes support a likely relationship between BD and the X chromosome.

Muscular dystrophy (MD) is a disease that clinically presents with a progressive and irreversible loss of muscle function. It is defined into two groups, Duchenne and Becker. It is an X-linked recessive disease which develops due to corrupted dystrophin protein, which is coded by Xp21 and is found in brain and muscle tissue. Dystrophin is synthesized in the central nervous system, particularly in the cerebral neocortex, hippocampal region and cerebellar purkinje cells (9,10). The role of dystrophin in the brain has been investigated in detail and it has been suggested that changes in the dystrophin gene might be a cause for cognitive impairment (11). Studies conducted in recent years have detected some cognitive function impairments in patients with Duchenne-type MD (12).

We are not aware of any reports concerning the association between BD and MD. The presence of both disorders in the present patient case and the fact that the patient's mother had BD was worthy of investigation. Since we had limited facilities for genetic analysis, the dystrophin gene was investigated in the patient and his brother, who also has MD, using a PCR method alone.

CASE REPORT

The patient was a 35-year-old, single male, and a primary school graduate. He was unemployed because of MD, supporting himself with a subsidy for disabled people, and living with his mother and brother in a village. He attended our policlinic in September 2011 with the signs of a manic episode. Complete remission was achieved within 2 months with lithium and zuclopenthixol. However, he developed a mild compulsion for cleanliness and symmetry three months later. His muscular dystrophy had been a concern of his family during early childhood, but they had rarely brought the patient to a university hospital since he was 10 because of their low socio-economic status. He had been diagnosed with MD based on examinations performed in the above-mentioned hospital. The cleanliness and symmetry obsessions started when he was 15, but the patient had refused psychiatric support until two years ago. He was diagnosed to have obsessive compulsive disorder (OCD) two years ago and clomipramine had been commenced, but he developed a manic episode after a short time. Clomipramine was discontinued and the manic episode was treated with olanzapine and quetiapine. Another manic episode occurred a year ago, when clomipramine was commenced once again for OCD. The case described clomipramine as "the drug making me talk". The current manic episode of the patient started spontaneously.

The mother was a 58-year-old, primary school graduate housewife. She first experienced a depressive episode in 2004 followed by a manic episode in 2005 and begun to receive valproate. She had been using valproate irregularly and had experienced a manic episode again in 2008. Thereafter she began to use valproate regularly but presented to the policlinic with depressive symptoms a year ago, citalopram 20 mg was added to her treatment. However, no improvement was observed in her depressive symptoms. Thyroid function tests were performed during her admission in September 2011, and she was directed to the endocrinology policlinic based on a low TSH level. The clinical presentation of hyperthyroidism disappeared within approximately three months with anti-thyroid drugs and her depressive symptoms also disappeared in line with recovery in her hyperthyroidism. Her family history revealed

no psychiatric disorder.

The father was a primary school graduate farmer. He died of glioblastoma multiforme a year ago when he was 68 years old. His personal and family histories revealed no psychiatric disorder.

The younger brother was a 25-years-old, single male. He was unemployed because of MD and receiving a subsidy for disabled people. Psychiatric examination was unremarkable and his personal history revealed no psychiatric disorder.

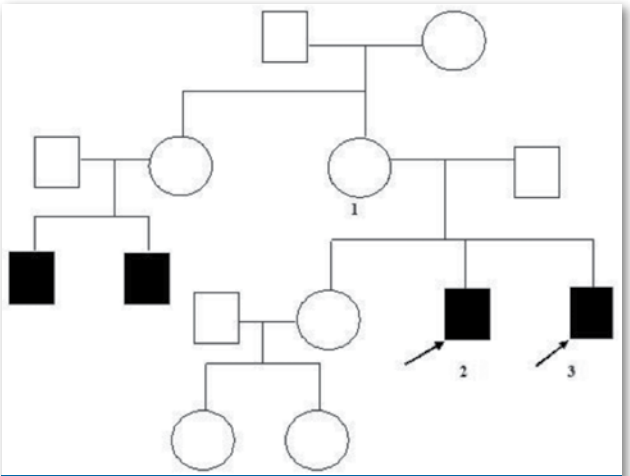

Figure 1: Pedigree of probands; it is known that there is bipolar disorder in the patients number 1 and 2, muscular dystrophy in the patients number 2 and 3.

The elder sister was a 38-year-old primary school graduate female. She was married and had two girls. She is a farmer too. Her personal history revealed no psychiatric disorder.

MD was present also in his two cousins (sons of his maternal aunt).

Genetic Analysis

Molecular analyses were done in the cases with MD and dystrophin gene defects were analyzed via a PCR method. DNA isolation was performed in peripheral blood samples obtained from both male MD patients (13). A PCR was performed using primaries defined before by Abbs et al. (14). The 1, 3, 4, 6, 8, 12, 13, 17, 19, 43, 44, 45, 47, 50, 51, 52, 60 and Pm regions, which have been defined in the dystrophin gene region, were separately analyzed.

The PCR analysis revealed deletions in the 45, 47 and 48 exons of case number 2 and in the Pm, 45, 47, 48 and 51 exons of case number 3. The mother is known to be a heterozygote; however, deletions in the mother could not be detected via PCR. Detection of the mother's deletion requires strand analysis. The results are demonstrated in Figure 2. The PCR was performed in a 25-mL volume with 100 ng DNA, 100 mm deoxynucleotide triphosphates

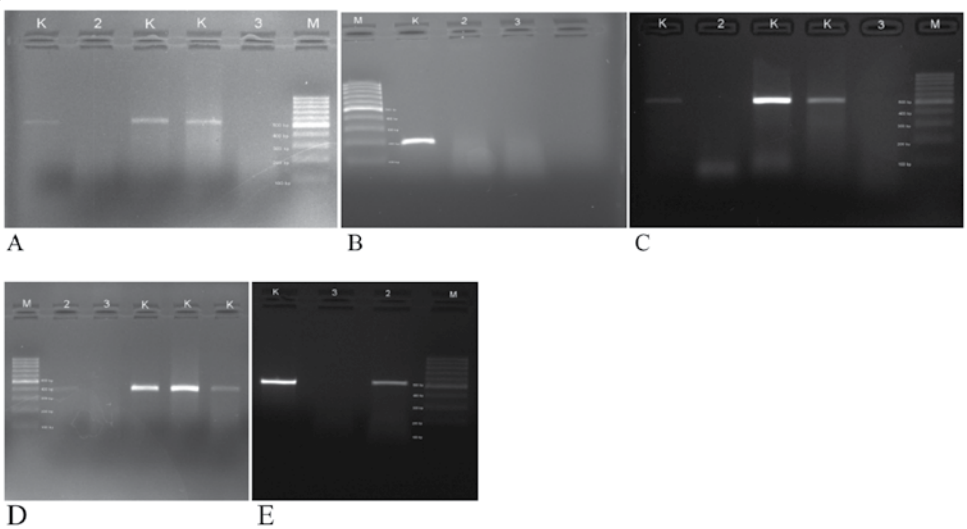

Figure 2: Exon regions of the cases number 2 and 3 and the control were evaluated individually. Figure A shows exon 45 (547 bp), B shows exon 47 (147 bp), C shows exon 48 (506 bp), D shows exon 51 (388 bp), and E shows Pm region (535 bp). (Analysis was repeated at least three times for each exon)

(dNTPs), 20 pmol of each primer, 1.5 mM MgCl2, 1 X PCR buffer with (NH4)2SO4 (Fermentas, Vilnius, Lithuania), 10% dimethyl sulfoxide (DMSO) and 2 U Taq DNA polymerase (Fermentas, Vilnius, Lithuania). Amplification was performed on an automated Thermal Cycler (Techne Flexigene, Cambridge, UK). The genotyping of the CHRNA4 gene polymorphisms was determined by fragment separation at 120 V for 40–50 minutes on a 2% Agarose gel containing 0.5 mg/mL ethidium bromide. A 100-bp DNA Ladder (FermentasVilnius, Lithuania) was used as a size standard for each gel lane. The gel was visualized under UV light using a gel electrophoresis visualizing system (Vilber Lourmat, Deutschland). PCR conditions were: 2 min for initial denaturation at 95°C, 35 cycles at 95°C for 45 sec for denaturation, 1 min at 56°C for annealing and 90 sec at 72°C for extension, followed by 7 min at 72°C for final extension.

DISCUSSION

Which makes this case interesting and important is the co-existence of muscular dystrophy and bipolar disorder, which are known to be genetically transmitted. Whereas MD shows X-linked recessive transmission with a definitely proven pathogenesis,. the genetics of BD have not been clearly demonstrated yet. The fact that the mother of the case had BD and transmitted the disease to her son and that she also transmitted MD to her son over the X chromosome made us think that the X chromosome might have played an important role in the genetic etiopathogenesis of BD.

It was determined that the present case had a dystrophin gene mutation and that BD had been transmitted to the boy number 2 from the mother marked as number 1 in the pedigree. There are studies supporting that BD might have been transmitted by certain genes on the X chromosome; however, the gene regions involved have not been clarified yet (5-7).

It is quite difficult to find a clear answer to the question "Are extensive dystrophin gene mutations on the X chromosome likely to induce bipolar disorder in the present case?" However, the association between Dystrophin Binding Partner (DTNBP1, dysbindin), which forms a complex by binding to dystrophin protein in the central nervous system, and schizophrenia has been reported (15). In that case, the dystrophin defects that cause MD might have had a role in the activity of DTNBP1, which binds to dystrophin. In other words, the inheritance of the disease from the mother, the presence of extensive dystrophin defects together with MD in both male children, and a bipolar mother might have enhanced the proclivity to bipolar disorder in one male child. In addition, the reason for the absence of bipolar disease at this time in the number 3 male subject can be explained by his being younger and by the absence of antidepressant use that is likely to induce mania. Nevertheless, the first manic episode of the present case, which was triggered by antidepressants, had first developed at an age of 33 years. Thus, it is thought that the brother of the present case has a substantial proclivity to BD.

According to our overall results, the presence of different deletions in the brothers is a conspicuous finding. Lee et al. conducted a study in 2012 and found similar results. Deletion was detected in different regions in two brothers diagnosed to have Duchenne-type MD (16). Accordingly, the absence of bipolar disorder at this time in number 3 subject, who had more deletions, is also conspicuous for the present case.

In conclusion, it was thought that BD, as well as MD that presented itself with mutations on the dystrophin gene, might have developed due to the X chromosome transmitted from the mother.

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