

[CASE REPORT]

X-linked Intellectual Disability with Novel Chromosome 9p12-pter Unbalanced Translocation on Chromosome Xp

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Abstract:

Abnormalities in genes on the X chromosome or large defects in the X chromosome itself cause X-linked intellectual disability. The proband was a 27-year-old man. His medical history included strabismus, cryptorchidism, and severe intellectual disabilities. He also had epilepsy. His mother seemed to have slight intellectual disability. A physical examination revealed malformations. The lateral and fourth ventricles were dilated using computed tomography. CGG repeats in the 5' untranslated region of *FMRI* gene were normal. G-banding and spectral karyotyping revealed a novel unbalanced X-autosomal translocation, with a karyotype of 46,Y,der(X)t(X;9)(p22.33;p12); distal trisomy of 9p and distal Xp nullisomy.

Key words: X-linked mental retardation, 9p trisomy, Xp nullisomy, X-autosomal translocation

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Introduction

Abnormalities in genes on the X chromosome or large defects in the X chromosome itself cause X-linked intellectual disability. Although men with gene deletions on the X chromosome show severe intellectual disability, their mothers have only slight or mild cognitive impairment because of skewed X-chromosome inactivation. The brothers of their mothers have also been shown to have severe cognitive disabilities. The most frequent cause of X-linked intellectual disability is fragile X syndrome, which accounts for 2.4% of all intellectual disabilities. CGG trinucleotide repeat expansion in fragile X mental retardation 1 (*FMRI*) is its cause (1).

We encountered a case of suspected X-linked intellectual disability. A chromosome analysis revealed unbalanced X-autosomal translocation.

Case Report

A 27-year-old man presented with burn injury to the anterior chest wall. He was discovered unconscious in the bathtub and exposed to hot water. Since he had intellectual dis-

ability and epilepsy, he was treated with antiepileptics in the department of pediatrics at another hospital. In the past several years, he had stopped taking medication for unknown reasons. The patient was admitted to the department of dermatology. The neurological department was consulted to diagnose the cause of the faintness. He was alert when we saw him the next day after admission. He could speak some easy words and obey simple verbal commands, but could not explain his medical history. We therefore obtained his medical history from his mother, who was also in attendance. However, her response was poor and unsatisfactory.

The next day, we interviewed his father. The patient's parents were non-consanguineous. He had a healthy brother, but his mother's brother had a psychological disorder. He had been born at term without any complications during pregnancy. His birth body weight, height, and head circumference had been 2,850 g, 46.7 cm, and 32.7 cm, respectively. His medical history included strabismus, cryptorchidism, and severe intellectual disability. On admission, his body weight and height were 85 kg and 157 cm, respectively. The patient had a well-defined nose, dark brown hair, and brown eyes. There were no finger deformities. The genitalia were male with a small penis and scrotum. Pubic hair was present. He had flat feet. Neither paralysis nor ataxia of

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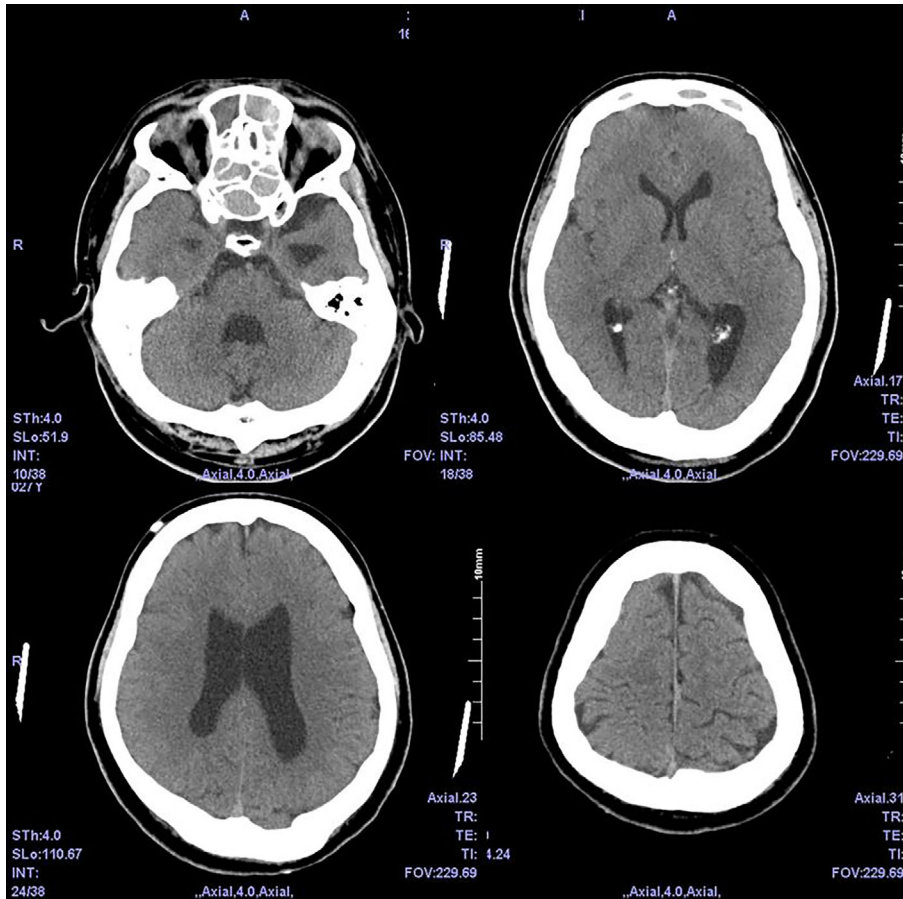


Figure 1. Computed tomography of the patient. Although dilation of the lateral ventricles and the fourth ventricle were found, no cortical dysplasia was observed.

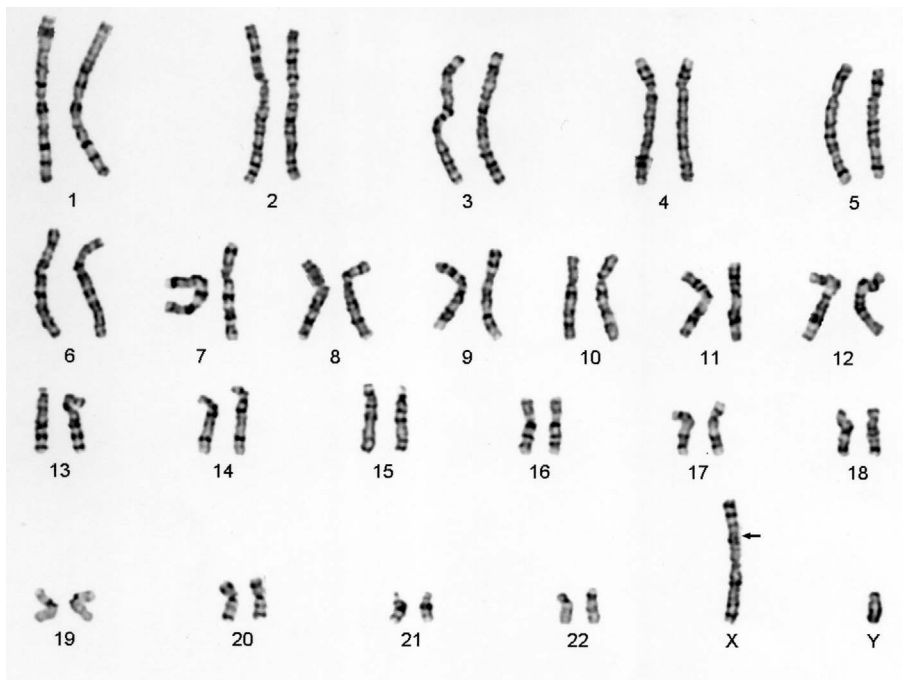


Figure 2. The G-banding technique showed translocation of an unknown origin chromosome on Xp (arrow).

the limbs was observed. He was able to walk normally without assistance.

Routine blood tests revealed an increased white blood cell count and C-reactive protein levels, probably due to burn in-

jury. Other blood test results were normal. Electrocardiography (ECG) showed counter-clockwise rotation. Echocardiography did not reveal any cardiac anomaly. Computed tomography of his head showed dilation of the lateral ventricles and fourth ventricle without cortical dysplasia, indicating developmental delay of the cerebrum and cerebellum (Fig. 1). Electroencephalography showed slow background waves but no epileptic discharges. Holter ECG did not show the existence of arrhythmia or cardiac conduction block causing the syncope. After admission, generalized convulsions were observed by a physician.

The fact that he was a severely intellectually disabled man with a mildly disabled mother suggested an X-linked inheritance. With informed consent from his father, we checked for chromosomal abnormalities and fragile X genes. The G-banding technique revealed translocation of the origin-unknown chromosome on the partially deleted Xp (Fig. 2). Fluorescent *in situ* hybridization using 1p, 1q, Xp, Yp subtelomeric probes, and X centromeric probe showed the absence of the Xp signal (Fig. 3). Spectral karyotyping clearly

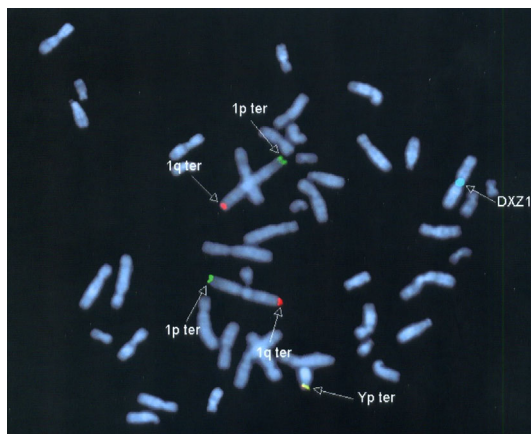


Figure 3. Fluorescence *in situ* hybridization using 1p, 1q, Xp, Yp subtelomeric probes and X centromeric probe (DXZ1) showed absence of Xp signal.

showed that the unknown origin was chromosome 9 (Fig. 4). Conversely, CGG repeats on the 5' untranslated region of *FMR1* gene were normal according to a restriction enzyme assay (data not shown). Ultimately, the patient was diagnosed with 46,Y,der(X)t(X;9)(p22.33;p12), distal trisomy 9p, and distal nullisomy Xp. His father and mother did not agree to undergo a chromosomal analysis.

He was treated with valproate and later in combination with levetiracetam because of recurrence of complex partial seizures. At present (35 years old), he can not complete the mini-mental state examination. His intelligence quotient as determined by the Kohs block-design test was 56.25.

Discussion

Trisomy 9p is one of the most common partial trisomies in newborns. However, the unbalanced translocation of 9p on the X chromosome is rare. Although 11 cases of unbalanced X; autosome translocations have been reviewed by Wu, et al. (2), there was only 1 case of unbalanced t(X;9) translocation with a karyotype of 46,X,der(X)t(X;9)(q27;p23). To our knowledge, this is the first report of the karyotype of 46,Y,der(X)t(X;9)(p22.33;p12). The most similar karyotype was that reported by Menten et al. (3). Their case with a karyotype of 46,Y,der(X)t(X;9)(p22.32;p23) presented with intellectual disability, facial and finger deformities, short stature, and obesity. Although this was a case of *de novo* chromosomal rearrangement, our case was considered to have been inherited from his mother.

Whether the clinical symptoms of this patient arose from distal nullisomy of Xp or distal trisomy of 9p was not determined. Only two cases of distal Xp nullisomy have been reported in the English literature (3, 4). A boy described by Tiepolo (4) presented with malformed external genitalia. In contrast, distal 9p trisomy is more frequent. Guilherme et al. described the clinical features and chromosome breakpoints in 18 patients (5). The clinical features included microcephaly, brachycephaly, epicanthal folds, micrognathia,

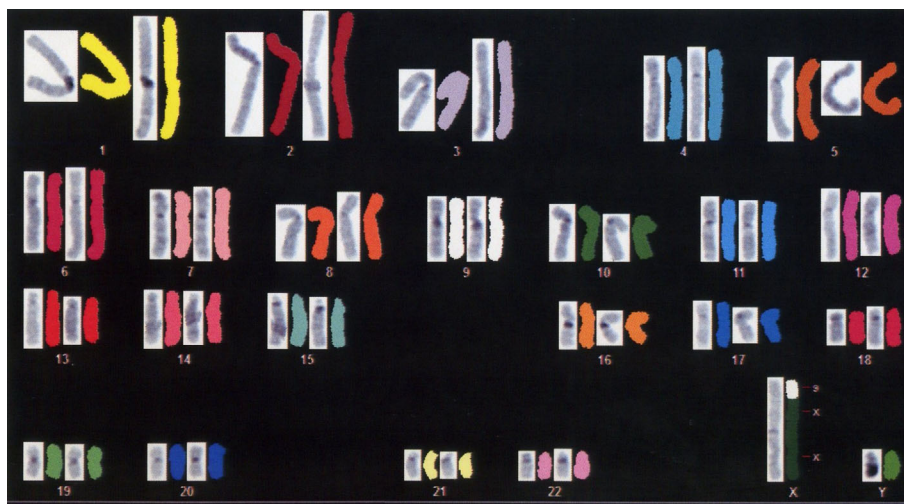


Figure 4. Spectral karyotyping revealed that the origin-unknown part was chromosome 9.

downslanting palpebral fissures, prominent/large nose, bulbous nasal tip, deep-set eyes, hypertelorism, low-set ears, malformed ears, downturned corners of the mouth, thin upper lip, short neck, short fifth finger, nail hypoplasia, clinodactyly, brachydactyly, neuropsychomotor development delay, hypotonia, growth delay, small penis, and speech delay.

In conclusion, we hope that the presented findings will be helpful in understanding X-autosome translocation by presenting clinical and cytogenetic data regarding a new unbalanced X;9 chromosome translocation. A chromosomal analysis should be considered in cases of X-linked intellectual disability.

The authors state that they have no Conflict of Interest (COI).

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