A De Novo Xp11.23 Duplication in a Girl with a Severe Phenotype: Expanding the Clinical Spectrum

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Abstract

Keywords

- ▶ duplication syndrome
- ▶ intellectual disability
- ▶ microarray analysis

The Xp11.22–p11.23 duplication syndrome was described in 2009 by Giorda et al and is characterized by intellectual disability, speech delay, and electroencephalography anomalies. We report a case of a 23-month-old girl who presented with epilepsy and global developmental delay and who had a small duplication at Xp11.23. The case we present here is the first case showing the clinical features of Xp11.22–p11.23 duplication syndrome only involving synovial sarcoma, X breakpoint (SSX) genes: SSX1, SSX3, SSX4, and SSX9. This case report contributes to an expanding clinical spectrum of Xp11.22–p11.23 duplication syndrome.

Introduction

The Xp11.22–p11.23 duplication syndrome was described in 2009 by Giorda et al and is characterized by intellectual disability (ID), speech delay, and electroencephalography (EEG) anomalies.¹ The characteristics of the syndrome were confirmed and further delineated by other authors over the years. Affected individuals share several common major features, including moderate-to-severe ID, early onset of puberty, foot abnormalities, language impairment, autistic behaviors, and seizures.

Females with duplications of the X chromosome are often clinically unaffected because the abnormal X is preferentially inactivated. In contrast, in most females with a Xp11.22–p11.23 duplication, the duplicated X chromosome is preferentially active, probably contributing to their clinical phenotype and suggesting that increased expression of a duplicated gene or genes might act as a selective factor on dividing cells.^{1–4}

Here, we report a case of a 23-month-old girl with a duplication of Xp11.23. This case report indicates that Xp11.2 duplications can be associated with a broader phenotype than previously described.

Case Report

A 23-month-old girl with epilepsy and global developmental delay was admitted to hospital. Family medical history of the patient was unremarkable. She was the first child resulting from in vitro fertilization to nonconsanguineous parents. She was born after an uncomplicated pregnancy and an uneventful delivery. Her birth weight was 3,100 g (25th–50th percentile), length was 50 cm (50th percentile), and head circumference was 35 cm (50th percentile).

On physical examination, the child had the following growth parameters: weight 10 kg (3rd–10th percentile), height 81 cm (3rd–10th percentile), and head circumference

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42 cm (3rd percentile). She had mild facial dysmorphic features, including bilateral epicanthic folds, down-slanting palpebral fissures, and broad nasal root. On neurological examination, she had generalized muscular hypotonia. She had not attained any developmental milestones, did not recognize her mother, and had no neck control. She was not able to follow instructions nor speak single words.

The first seizure manifested with subtle motor manifestations and perioral cyanosis that had lasted for 30 seconds on the third day of life. Interictal sleep video-EEG showed normal background activity. Echocardiogram and cranial magnetic resonance imaging were normal. Phenobarbital treatment was initiated. Her second seizure occurred 4 months later with eye deviation and loss of consciousness. Interictal sleep video-EEG revealed sharp and slow-wave discharges in the bilateral frontal regions (►Fig. 1). Carbamazepine was added to phenobarbital treatment. Afterward, she experienced one or two focal and/or generalized tonic-clonic seizures per month, usually precipitated by infections with fever. She had recurrent hospital admissions because of persistent pneumonia and seizures. Levetiracetam, topiramate, and clobazam were tried. Because of a lack of added efficacy, phenobarbital and levetiracetam were withdrawn.

Further detailed investigations included tandem mass spectroscopy, biotinidase activity, blood and urine amino acids, urine organic acids, plasma very long chain fatty acids, plasma vitamin B12, folate and homocysteine, serum immunoglobulin (Ig)G, IgA, and IgM levels, lymphocyte count, and antiendomysial antibodies were within normal range.

Fundus examination was normal. Analysis of *SCN1A* did not reveal any pathogenic mutations.

The TruSight Inherited Disease Sequencing Panel (Illumina Inc.) was used to identify a single gene cause for the patient's presentation. This gene panel included 552 genes associated with severe, recessive pediatric onset diseases. It did not reveal a pathogenic mutation.

For copy number changes, chromosome microarray analysis was performed using the Affymetrix GeneChip Array 750K. The patient was found to have a de novo 175-kb duplication at Xp11.23 (48.0–48.2 Mb, ►Fig. 2). The microarray analysis was reported as arr[hg19] Xp11.23p11.23 (48,099,939–48,275,555) × 3. The duplicated segment included synovial sarcoma, X breakpoint (*SSX*) genes: *SSX1* (312820), *SSX9* (300544), *SSX3* (300325), and *SSX4* (300326). Parental chromosome microarray analyses were normal.

The patient was admitted again at 25 months of age with a complaint of cough and fever. She died shortly after as a result of pneumonia.

Discussion

Here, we present a female with a Xp11.23 duplication with epilepsy and severe ID. This is the first case showing the clinical features of Xp11.22–p11.23 syndrome with duplication of only *SSX1*, *SSX3*, *SSX4*, and *SSX9* genes. The clinical features in our case overlap with the previously reported cases, but our patient's motor and developmental milestones were severely delayed and she suffered recurrent episodes of pneumonia.

Fig. 1 Interictal EEG demonstrating epileptiform discharges in the bilateral frontal regions. EEG, electroencephalography.

Fig. 2 Microarray analysis of the patient with duplication at Xp11.22–11.23.

Chromosomal imbalances and copy number variations are the most common genetic causes of ID and congenital anomalies. The widespread use of array comparative genomic hybridization (aCGH) in diagnostics and research has led to identification of a growing number of microdeletion and microduplication syndromes often with recognizable phenotypes.⁵ For this reason, evaluation by aCGH or molecular karyotyping is a first-line recommended investigation for children with developmental delay/ID.⁶

Chromosome region Xp11.22–p11.23 includes *SHROOM4* (300579), *KDM5C* (314690), *IQSEC2* (300522), and *HUWE1* (300697). Mutations within and copy number variation of these genes have been associated with ID. Santos-Rebouças et al reported two unrelated individuals with syndromic ID with duplications at Xp11.22 encompassing *HUWE1*.⁷ Fieremans et al described a female with ID who had a 0.4-Mb microdeletion at Xp11.22 including the ID genes *KDM5C* and *IQSEC2*.⁸ Autism spectrum disorder is frequently reported in patients with Xp11.22–p11.23 duplication syndrome. Edens et al reported two females with autism due to Xp11.22–p11.23 duplications. They suggested that duplication of *GRIPAP1*, *FAM120C*, and *WNK3* were the key genes associated with pathogenicity in these females.⁹

In our patient, the duplicated segment included *SSX1* (312820), *SSX9* (300544), *SSX3* (300325), and *SSX4* (300326). These genes are members of the synovial sarcoma X breakpoint (*SSX*) gene family. *SSX* gene family members normally act as transcriptional regulators and also fusion partners for the *SYT* gene in the t(X;18) translocation that underlies synovial sarcomas.¹⁰ Chromosome region Xp11.22–p11.23 contains

many MIM annotated ID genes; however, mutation/copy number variants in *SSX* genes have not been identified as ID causing. Although *SSX* genes have not been associated with ID, they are frequently duplicated in individuals with Xp11.22–p11.23 duplication syndrome.^{1,11}

There is no clear correlation between the degree of ID and the size of the Xp11.23 duplication or the X chromosome inactivation pattern. Even in patients with duplications of the same size and identical pattern of X chromosome inactivation, cognitive abilities can vary between normal and severe ID.^{1,12} Grams et al described a 6-year-old girl with a 4.5-Mb duplication at Xp11.23 with mild dysmorphic features and mild ID. They also reported a 1-year-old boy with a 61-kb duplication at Xp11.23 with global developmental delays, including motor, verbal, and poor feeding.¹³ The female presented here had a very small duplication of 175 kb yet had severe ID.

Seizures are the other common features of the Xp11.23 duplication syndrome. EEG abnormalities that have been described in individuals with this duplication include focal spike and waves activated during sleep with frequent generalization, continuous spikes and waves during slow sleep, hypsarrhythmia, and generalized spike-and-wave abnormalities.^{14,15} Evers et al reported monozygotic twins with multiple tonic-clonic seizures whose EEG had generalized spike-and-wave discharges. The seizures of both twins were well controlled by therapy with sodium valproate and no further seizures occurred.¹⁶ Our patient developed medically refractory epilepsy. She experienced one or two focal and/or generalized tonic-clonic seizures per month, usually associated with infections with fever. The first EEG at 3 days of age showed no interictal

epileptiform activity, but subsequent serial EEGs showed focal spike and waves activated during sleep.

Infections have not been commonly reported in individuals with the Xp11.22–p11.23 duplication syndrome. Evers et al described a 10-year-old girl with recurrent otitis media leading to bilateral hearing loss. They also reported a female with febrile seizures.¹⁶ Our patient had recurrent hospital admissions because of pneumonia and fever. Serum IgG, IgA, and IgM levels and lymphocyte count were within normal range.

The functions and clinical effects of dosage changes of SSX genes are not fully understood. It is known that the protein products of these genes are involved in spontaneous humoral and cellular immune responses in cancer patients, and thought to be targets for vaccine-based cancer immunotherapy. Thus, we can speculate that duplication of *SSX1*, *SSX9*, *SXX3*, and *SXX4* may have contributed to our patient's phenotype by disruption of these normal functions.¹⁷

In summary, we have presented a girl with a very small Xp11.2 duplication. The most important phenotypic finding is that she presented with more severe ID and severe infections than previously reported individuals with Xp11.22–p11.23 duplication syndrome. This case report contributes to an expanding clinical spectrum of patients with Xp11.2 duplication.

Conflict of Interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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