XP22.33-P11.4 DUPLICATION AND 46, X+MAR GONADAL DYSGENESIS IN A PATIENT WITH EPILEPSY, DYSMORPHISMS, HYPOTONIA AND INTELLECTUAL DISABILITY, A CASE REPORT

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INTRODUCTION

Xp duplication is a rare condition in both males and females, and findings in affected females include short stature, facial anomalies, mental retardation, hypotonia, and myoclonic epilepsy.[1,2] Gonadal dysgenesis is a subtype of interrupted sexual development disorders that refers to a variety of clinical conditions in the abnormal development of fetal gonads, from normally virilized males to slightly less virilized males, indeterminate phenotype, and normal phenotypic females.[3] We report the Xp22.33-p11.4 duplication and 46, X+mar gonadal dysgenesis in a patient with epilepsy, mental retardation, dysmorphisms, hypotonia and congenital heart disease.

CASE REPORT

A 6-month-old girl who was diagnosed with intrauterine growth retardation (IUGR), gonadal dysgenesis, bilateral sensorineural hearing loss and atrial septal defect secundum in the neonatal period, presented with myoclonic jerks and neurodevelopmental retardation. There was no consanguinity between the parents. Neurological examination was reported normal except of central hypotonia that presented for a month and dysmorphic features (low set ears, hypertelorism, high forehead). Complete blood count, liver and kidney function tests, creatine phosphokinase were within normal limits. Further detailed investigations included tandem mass spectroscopy, blood and urine amino acids, urine organic acids, ammonia, lactate, plasma vitamin B12, folate and homocysteine were within normal range. Brain magnetic resonance imaging and electroencephalogram were normal. The cytogenetic analysis of the case with female external and internal genital organ phenotypes was found to be 46,X,+mar (SRY+) with marker chromosome (**Fig.1**).

In order to determine the origin of the marker chromosome, the presence of the SRY region was demonstrated by quantitative fluorescence-PCR (QF-PCR) and fluorescence in situ hybridization (FISH) testing was performed with the SHOX probe. Signal belonging to the SHOX region was detected at both ends of the marker chromosome. With these results, it was thought that the marker chromosome might be a derived Y chromosome containing genomic material belonging to the X chromosome. A microarray was performed to obtain additional data. The patient was found to have 39 Mbp duplication at Xp22.33-p11.4 containing 112 OMIM genes (**Fig.2**). The microarray analysis was reported as arr[hg19] Xp22.33p11.4(168,546-39,013,567)x2. Parental chromosome microarray analyses were normal. Levetiracetam was started as an antiseizure medication but the treatment was adjusted as valproic acid because of increased in seizures in the form of generalized tonic-clonic beats. She is still under follow-up in our clinic.

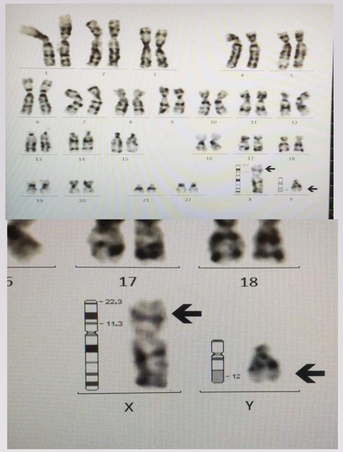

Fig. 1: Derived Y region with duplication on the X chromosome

DISCUSSION

Although there are many series related to Xp duplication in the literature, no cases of Xp22.33-p11.4 duplication and 46, X+mar gonadal dysgenesis have been reported before. The detected duplicated segment of our patient included many genes classified as ‘disease genes’ in the OMIM database of genetic disorders (http://www.omim.org/). These genes were also found to be significant in our case; such as: **CDKL5** (OMIM 300203) was associated with Rett syndrome, epileptic encephalopathy; **OFD1** (OMIM 300170) was associated with Joubert syndrome characterized by hypotonia, cerebellar ataxia and developmental delay; **NLGN4** (OMIM 300427) was associated with autism, intellectual disability, Asperger syndrome; **RPS6KA3** (OMIM 300075) was associated with sensorineural hearing loss and X-linked intellectual developmental disorder; **AP1S2** (OMIM 300629), **FRMPD4** (OMIM 300838) and **GLRA2** (OMIM 305990) were associated with X-linked intellectual developmental disorder; **NR0B1** (OMIM 300473) was associated with gonadal dysgenesis.[2,4-8]

Fig. 2: Derived Y region with duplication on the X chromosome

In addition, many other genes within the duplication play an important role in the nervous system and have been found to be associated with neurodevelopmental disorders. The phenotype and clinical features as at our case are shaped by the effects of the genes contained in the copy number changes in cases with this type of microdeletion and microduplication. In our case, we emphasize the importance of evaluating the clinical features and phenotype of the case with performing different genetic studies.

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