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When Extra Gene Speaks: Genotype-Phenotype Correlation in Partial Duplication of Chromosome 13, A Case Report

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Abstract: ***Partial duplication of chromosome 13q is a rare chromosomal disorder associated with congenital anomalies, neurodevelopmental impairment, and refractory epilepsy. We report a 6.5-year-old male who presented with dysmorphism, seizures and developmental delay. Child was born at term gestation with low birth weight to non-consanguineous parents, with three prior maternal spontaneous abortions. Brief upper-limb flexion episodes began on day 3 of life but were evaluated only at 7 weeks of age during an admission for lower respiratory tract infection, when valproate and clobazam were initiated. Despite normal early neuroimaging, global developmental delay persisted. Over the last 6-7 months, he developed increased seizure frequency and loss of milestones. Examination showed microcephaly with trigonocephaly, right irido-fungal coloboma, bilateral post-axial polydactyly, bilateral undescended testes with right inguinal hernia, and mild right-sided sensorineural hearing loss. Metabolic workup was normal. Repeat MRI brain remained unremarkable, while EEG showed generalized epileptiform discharges with sleep activation (SWI >60%). Abdominal ultrasonography and echocardiography were normal. Whole-exome sequencing revealed a pathogenic duplication of chromosome 13q13.3-q34; parental karyotypes were normal, confirming a de novo event. Seizures improved with zonisamide and clobazam, and the child was started on physiotherapy while awaiting hernia repair. This case highlights the need for early genetic evaluation in children with syndromic features, refractory epilepsy, and developmental delay to enable accurate diagnosis and counselling.***

Keywords: Chromosome 13q duplication, Developmental delay, Early-onset epilepsy, Dysmorphism.

1. Introduction

Chromosome 13q duplication is a rare genomic imbalance characterized by partial trisomy of the long arm of chromosome 13, involving multiple genes which are essential for neurodevelopment, craniofacial morphogenesis, ocular formation, limb patterning, and neuronal signaling pathways.

The phenotypic spectrum is wide, reflecting variations in duplication size and gene content. Duplications involving the distal and mid-distal region (q13-q34) have been associated with early-onset neurodevelopmental disorders, refractory epilepsy, congenital anomalies, and distinctive dysmorphic features.

2. Clinical Summary

We present a case of 6.5 years male child, born at term gestation by normal vaginal delivery with a birth weight of 2.4 kg to non-consanguineous parents. Antenatal and intrapartum periods were uneventful, though the mother had three early (first trimester) spontaneous abortions.

The parents noted brief flexion movements of the upper limbs on day 3 of life, occurring 10-12 times per day, which remained unevaluated until the child presented to healthcare at 7 weeks of age with lower respiratory tract infection and was diagnosed with seizure disorder. MRI brain was done, which was unremarkable. Child was started on valproate (@ 20mg/kg/day in 3 divided doses). Despite treatment, the child exhibited global developmental delay with minimal milestone acquisition. Seizure persisted till 3 years of age with similar simiology, despite on 3 anti-epileptic medications including valproate, phenytoin and clobazam at appropriate doses. Child was started on Topiramate at 3 years of age which had a remarkable control in seizure frequency.

Child remained relatively seizure-free for nearly three years, after which he developed worsening seizure frequency and regression of developmental skills, a pattern paralleling the progressive neurological course described in some distal 13q duplications.

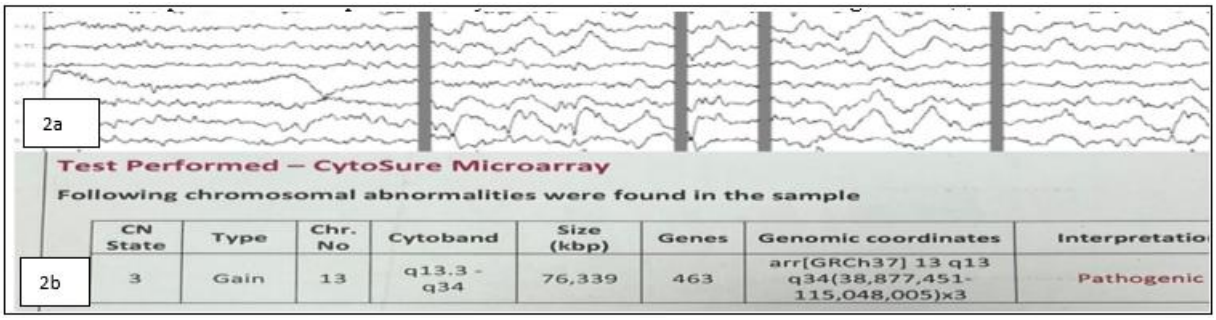
On evaluation, he demonstrated multiple dysmorphic features, including microcephaly with trigonocephaly (Figure 1a, 1b, 1c), low set ears, right irido-fundal coloboma, bilateral post-axial polydactyly of the lower limbs, and bilateral undescended testes with right inguinal hernia (Fig 1d). Post-axial polydactyly- widely reported in distal 13q duplications—is recognized as a hallmark phenotypic feature (1). Ocular anomalies, particularly coloboma, have also been described in association with duplications involving the mid-distal 13q segment (2). Child exhibits a moderate underweight (weight=14.8Kg) and short stature (Height = 104cm) with microcephaly (Head circumference =49.8cms).

Figure 1: Facial dysmorphism [(a)microcephaly, (b) trigonocephaly, (c) low set ears], (d) right inguinal hernia.

Investigations

Metabolic evaluation including blood sugar, serum lactate, serum ammonia, blood pH, urinary ketones was normal. Metabolome analysis by urinary GCMS (Gas chromatography mass spectrometry) and serum TMS (Tandem Mass Spectrometry) was normal. Audiological assessment BERA (Brainstem Evoked Response Audiometry) revealed mild right-sided sensorineural hearing loss, consistent with reported sensory deficits in some 13q duplication cases. EEG (Electroencephalogram) demonstrated generalized epileptiform discharges with abundant spike-wave and polyspike-wave activity (Figure 2a) with sleep-activated discharges (SWI >60%), reflecting an epileptic encephalopathy. A repeat neuroimaging (MRI) at 6.5 years remained normal, consistent with reports that neurodevelopmental impairment in 13q duplication may occur even without major structural brain abnormalities**.** Drug-resistant epilepsy and abnormal EEG patterns are frequently described among individuals with distal 13q duplications (1).

Whole-exome sequencing identified a pathogenic duplication at chromosome 13q13.3-q34 with duplication spanning of 76,339 kbp on chromosome 13 (Figure 2b). Parental karyotypes were normal, indicating a de novo event, like most reported cases where distal duplications arise spontaneously without familial balanced rearrangements (1).



CN State	Type	Chr. No	Cytoband	Size (kbp)	Genes	Genomic coordinates	Interpretatio
3	Gain	13	q13.3 - q34	76,339	463	arr[GRCh37] 13 q13 q34(38,877,451-115,048,005)x3	Pathogenic

Figure 2: (2a) showing generalized epileptiform discharges with abundant spike-wave and polyspike-wave activity. (2b) showing pathogenic gain of chr 13 q13.3-q34 region.

Seizures improved with zonisamide and clobazam, and child was given rehabilitative care including physiotherapy, anti-gastro esophageal reflux medications, speech therapy and planned for surgical repair of the inguinal hernia. Genetic counselling was given to the parents.

3. Discussion

We report the case of a 6.5-year-old male child with confirmed partial duplication of chromosome 13q13.3-q34, who presented with developmental regression and progressively increasing seizures. The combination of developmental delay, early-onset epilepsy, dysmorphic features, congenital anomalies, and normal neuroimaging is highly characteristic of chromosome 13q duplication syndromes. Previous reports describe psychomotor delay, intellectual disability, craniofacial dysmorphism, microcephaly, post-axial polydactyly, hypotonia, and epilepsy as the most consistent findings in affected individuals (1). Additional features such as callosal dysgenesis, leukoencephalopathy, cortical dysplasia, and structural brain malformations have also been documented, although neuroimaging may remain normal in some patients. Epilepsy is common and may be related to dysfunctional neuronal signaling and is often difficult to control with standard antiseizure medications (1).

Several genes within the 13q13-q34 interval including COL4A1, COL4A2, SOX21, EDNRB, PROZ, GAS6 and GPC5/GPC6, are thought to contribute to the neurological, ocular, vascular, and skeletal manifestations. Overexpression of *COL4A1* and *COL4A2* has been associated with cerebrovascular fragility and white-matter changes, while *SOX21* is implicated in neuronal differentiation and myelination (3). The presence of ocular anomalies such as coloboma, limb malformations including hexadactyly/post-axial polydactyly, and craniofacial dysmorphism such as long philtrum, frontal bossing, and hypertelorism is frequently noted in distal duplications (2).

This case reinforces the need for early genomic evaluation in children presenting with syndromic epilepsy and congenital anomalies, as early diagnosis facilitates appropriate prognostication, surveillance, and genetic counselling.

References

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