

CASE REPORT

Infantile spasms with periventricular nodular heterotopia, unbalanced chromosomal translocation 3p26.2 -10p15.1 and 6q22.31 duplication

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Introduction

Infantile spasms are a catastrophic seizure disorder usually associated with the epileptic encephalopathy West syndrome characterized by epileptic spasms, hypsarrhythmia, and developmental regression [1]. While Down syndrome and tuberous sclerosis complex are well-known genetic causes, mutations in numerous other genes have been identified in recent years including *ARX*, *CDKL5*, *FOXG1*, *GRIN1*, *GRIN2A*, *MAGI2*, *MEF2 C*, *SLC25A22*, *SPTAN1*, and *STXBPI* [2–4]. West syndrome has been rarely reported in children with periventricular nodular heterotopia, causes of which include mutations in the *FLNA* and *ARFGF2* genes [5, 6]. We report a case of West syndrome with periventricular nodular heterotopia and an unbalanced chromosomal translocation between chromosomal bands 3p26.2 and 10p15.1 with additional 6q22.31 duplication. These regions do not contain known genes for periventricular nodular heterotopia or infantile

Key Clinical Message

Patients presenting with infantile spasms, dysmorphic features, and periventricular nodular heterotopia may benefit from genetic copy number variation microarray, or whole-exome sequencing to identify candidate genes. This will allow personalized diagnosis and prognostication and the eventual understanding of single and combined gene functions in brain health and disease.

Keywords

Infantile spasms, periventricular nodular heterotopia, personalized medicine.

spasms. We review the set of candidate genes affected in our patient and the literature on similar chromosomal rearrangements. This type of personalized analyses contributes to the further understanding of genes and pathways underlying the idiopathic infantile spasms.

Case Report

A 5-month-old, infant male presented with infantile spasms and was initially treated with high-dose vigabatrin and pyridoxine. Within 3 weeks, he had responded clinically with resolution of spasms, but not electrographically. High-dose adrenocorticotropic hormone (ACTH) was added and within 2 weeks, the hypsarrhythmia resolved. He developed generalized dystonia, tremor, and chorea at 7 months of age, likely an iatrogenic effect of vigabatrin as it resolved with vigabatrin removal and replacement with levetiracetam.

Antenatal history was uneventful with protective serology, no toxin exposure, and normal antenatal

ultrasounds. His mother had previously undergone a pregnancy termination at 13-week gestation due to a fetal diagnosis of trisomy 13. Our patient was born at term via spontaneous vaginal delivery with Apgar scores of 9 and 10 at 1 and 5 minutes. Birth weight was 3.05 kg (50th percentile) and length 50.8 cm (65th percentile). He was noted to have a short tongue, bilateral undescended testes, and a sacral dimple. Spinal ultrasound was normal.

When he presented with infantile spasms, at 5 months, his weight was 7.6 kg (50th percentile), length 64.4 cm (15th percentile), and head circumference 42.5 cm (>3rd percentile). He had mild frontal bossing, epicanthal folds, hypertelorism (inner canthal distance 3 cm, outer canthal distance 8 cm, both >97th percentile), micrognathia, short tongue, and a sacral dimple. Respiratory, cardiac, and abdominal systems were unremarkable and testes had descended. Neurological examination was unremarkable. Magnetic resonance imaging (MRI) revealed left frontal periventricular subependymal gray matter heterotopia adjacent to the left frontal horn of the lateral ventricle, as well as signal changes within the brainstem and basal ganglia consistent with vigabatrin therapy. MR spectroscopy reported a glutamine/glutamate peak, which, again, is seen with vigabatrin. The spectroscopic and subcortical signal changes had resolved on a repeat MRI at 9 months. Screening metabolic workup was negative.

Regarding his development, he achieved expected milestones in gross and fine motor skills initially, however, after the age of 12 months, his delays were more obvious. He walked independently at 19 months of age. He did not develop a pincer grasp until after 13 months. His social, language, and cognitive development continue to be delayed when last evaluated at 20 months. He babbles but has no single words, does not point, and does not use imaginative play.

The nonspecific dysmorphic features suggested a genetic etiology and microarray testing using a genome build, NCBI build 36 (UCSC hg 18), identified a 5.203 Mb terminal deletion in the short arm of chromosome 10 in bands 10p15.3 to p15.1 (nucleotides 62,842–5,265,989), encompassing the *KLF6*, *AKR1C2*, and *AKR1C4* genes. Additionally, a 3.95 Mb terminal duplication was identified in the short arm of chromosome 3 between bands 3p26.3 and 3p26.2 (nucleotides 48,707–3,944,079), including the *CRBN* gene. The FISH and karyotype analysis confirmed that this deletion and duplication are due to an unbalanced chromosomal translocation between chromosomes 3 and 10 with an extra copy of 3pter having replaced 10pter on one derivative chromosome 10. FISH analysis of parental samples, were normal indicating that the translocation was de novo. Finally, the microarray testing had

Table 1. Affected genes in our patient, that is, the genes in the deletions and duplications of our patient in chromosomal bands 10p15.5-p15.1, 3p26.3-p26.2, and 6q22.

Gene	Copy number variant region	Function
ZMYND11	10p15.5-p15.1	Nuclear protein, variant-specific methylated histone reader that may fine-tune gene expression via transcription regulation.
IDI1	10p15.5-p15.1	Peroxisomal enzyme isopentenyl-diphosphate δ -isomerase 1 involved in cholesterol and fatty acid synthesis
ADARB2	10p15.5-p15.1	Ribosomal nucleic acid editing enzyme, which possibly plays a role in the regulation of substrate-specific RNA editing within the brain.
CHL1	3p26.3-p26.2	Adhesion molecule, which may regulate synaptic vesicle recycling, neuronal migration, and neurite growth in the developing brain.
CRBN	3p26.3-p26.2	Regulates adenosine monophosphate-activated protein kinase and new protein synthesis via the mammalian target of rapamycin signaling pathway
CNTN6	3p26.3-p26.2	Neural adhesion molecule of the contactin subgroup expressed in cortical neurons via excitatory glutamate synapses in the cerebellum and hippocampus
CNTN4	3p26.3-p26.2	Contactin neural adhesion molecule, which has been associated with spinocerebellar ataxia type 16
DIP2C	10p15.5-p15.1	Is expressed in the nervous system with unknown specific function
PLN	6q22	A calcium cycling protein and mediator of the β -adrenergic effect, which has been associated with idiopathic dilated cardiomyopathy.
KLF6	10p15.5-p15.1	A zinc finger-containing transcription factor and tumor suppressor. Mutations occur in prostate, colon, hepatocellular and gastric carcinomas, and astrocytic gliomas.
AKR1C2	10p15.5-p15.1	Mutations are associated with androgen biosynthesis defects causing 46XY disorders of sexual development and differentiation.
AKR1C3	10p15.5-p15.1	May precipitate castrate-resistant prostate cancer
AKR1E2	10p15.5-p15.1	A potential candidate gene for pediatric cataracts.
IL5RA	3p26.3-p26.2	Associated with sporadic Immunoglobulin A nephropathy.
LRRN1	3p26.3-p26.2	This gene is highly expressed in neuroblastomas with poor clinical outcome.
SUMF1	3p26.3-p26.2	Encodes alpha—formylglycine-generating enzyme causes multiple sulfatase deficiency.

also revealed a 0.273 Mb duplication in 6q22.31 (nucleotides 118,844,321–119,117,367) including the *PLN* gene. Early infantile encephalopathy panel was also ordered, which detected no pathogenic sequence changes in the *ARX*, *ARFGEF9*, *CDKL5*, *GRIN2A*, *MAGI2*, *PCDH19*, *PNKP*, *SCN1A*, *SLC2A1*, *SLC25A22*, or *STXBPI* genes.

Review of the literature identified 18 cases with 10p15.5-p15.1 deletions in size equal to or smaller than our patient's, of whom, 13 had adequate clinical descriptions [7, 8]. All 13 cases had developmental delay and two had seizures but none had periventricular nodular heterotopia or infantile spasms [7, 8]. There was one case with a 3p26.3-p26.2 duplication who presented with intellectual disability and seizures in the second year of life but had no periventricular nodular heterotopia or infantile spasms [9]. There were no clinical reports of 6q22 duplications comparable to that of our patient, and no cases combining two, or all three, of his chromosomal abnormalities.

Discussion

The developmental delay experienced by our patient, may be explained by the unbalanced chromosomal translocation between chromosomal bands 3p26.3-p26.2 and 10p15.5-p15.1. This is because patients with either of these lesions have been found to have intellectual disability. The causes of the periventricular nodular heterotopia and infantile spasms are unclear. West syndrome is usually the final common manifestation of a diverse list of structural, metabolic, and genetic etiologies presenting during the first year of postnatal development. The infantile spasms may be a secondary, nonspecific, result of the developmental pathology causing the periventricular nodular heterotopia or they may be the direct result of the combined deletion/duplication of genes specific to our patient's particular chromosomal aberration.

None of the reported cases with deletions or duplications similar to those constituting our patient's set of modifications had periventricular nodular heterotopia. It is possible that an oligogenic combination of missing/duplicated genes in our patient underlies his periventricular nodular heterotopia. Finally, it is possible that our patient's disease is caused by other unknown mutations, unrelated to his chromosomal abnormalities, which we have not seen because we did not analyze his entire genome sequence.

Table 1 lists the genes affected by his 10p15.5-p15.1, 3p26.3-p26.2, and 6q22 deletion/duplications, and their known functions. The first seven genes in our assessment

are the most likely to contribute to his phenotype. This is based on the known function of the proteins they encode. Genotype–phenotype studies such as this report, followed by whole-genome analyses, will allow personalized diagnosis and prognostication, together with the eventual understanding of single and combined gene functions in brain health and disease.

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