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Case Report

A Small Pure 3q25.1 Duplication Associated with Multiple Cerebral Organizational Defects

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Abstract: Duplications of the long arm of chromosome 3 most frequently occur in the context of other chromosomal copy number variations. Pure duplications of this region are exceedingly rare, varying widely in size and clinical presentation. Presented below is a case of a small pure duplication of the long arm of chromosome 3q25.1 associated with marked cerebral organization defects and the possible genotype/phenotype correlation between the two.

Keywords: 3q25.1, Pure Duplication, Copy Number Variant, Schizencephaly

1. Introduction

Duplications of the long arm of chromosome 3 were previously implicated as the cause of Brachmann-Cornelia de Lange Syndrome (OMIM 122470). A 3q duplication syndrome, thought to minimally involve 3q26.31-q27.3 and excluding 3q25-3q26.2, remains phenotypically heterogeneous [1-2]. This is because, to date, documented copy number variations (CNV) of this region have primarily occurred with other chromosomal translocations (both balanced and unbalanced), insertions, inversions, and neocentromeric analphic chromosomes, all involving duplications of varying amounts of chromosomal material [3-8]. Isolated, pure duplications of portions of chromosome 3q remain rare [9].

Of those patients who have pure duplications of chromosome 3q, central nervous system malformations range from nonexistent to profound. However, in these cases, the amount of duplicated genetic material also ranges widely, obviating the ability to precisely delineate genotype / phenotype relationships between the two.

Presented below is a patient who was found to have multiple cerebral organizational defects and a small pure 3q25.1 duplication involving approximately 322,000 base pairs. A review of central nervous system findings associated with pure duplications of this locus of chromosome 3q follows.

2. Case Report

This male patient was born via normal spontaneous vaginal delivery at 40 weeks gestation to a nonconsanguinous 32-year-old father and 20-year-old mother. During pregnancy his mother experienced abnormal bleeding at 3 and 5 months in addition to falling from an unknown height and being in a car accident at 7 months gestation. Fetal movements were normal throughout pregnancy. No infectious risk factors nor any issues with hyperglycemia or blood pressure were present during pregnancy.

The patient sat at 12 months of age and walked at 18 months of age, but was noted to have progressively worsening left-sided upper and lower extremity weakness which eventually prompted an evaluation by a geneticist and an accompanying radiologic workup.

At twenty-two months of age the physical exam was remarkable for: a wide forehead, a short wide upturned nose, underdeveloped auricular helices, bilateral telecanthus and epicanthal folds, long eyelashes, synophrys, mild retrognathia, and left-sided hemparesis with mild to moderate left-sided upper and lower extremity contractures.

Magnetic resonance imaging of the brain revealed closed-lip schizencephaly of the right parietal lobe (Figure 1), heterotopia of both frontal lobes (Figure 2), and pachygyria with absence of the septum pellucidum (Figure 3).

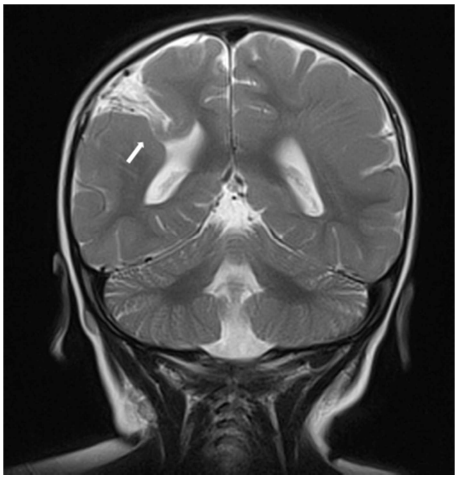

Figure 1. *Coronal T2 MRI image showing a cleft of the right-sided parietal lobe coated with thickened cortex which extends from the pial surface to the wall of the ipsilateral lateral ventricle consistent with closed-lip schizencephaly (white arrow).*

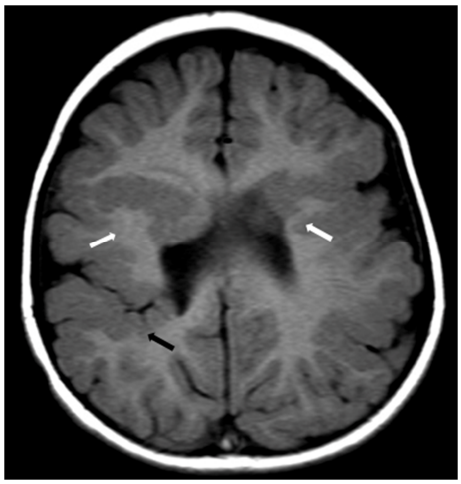

Figure 2. *Axial T1 MRI image showing enlarged dysplastic cortex with heterotopic subcortical and subependymal extension of grey matter in both fronal lobes consistent with pachygyria with associated heterotopia (white arrows). Also seen is an axial view of the right-sided parietal closed-lip schizencephaly (black arrow).*

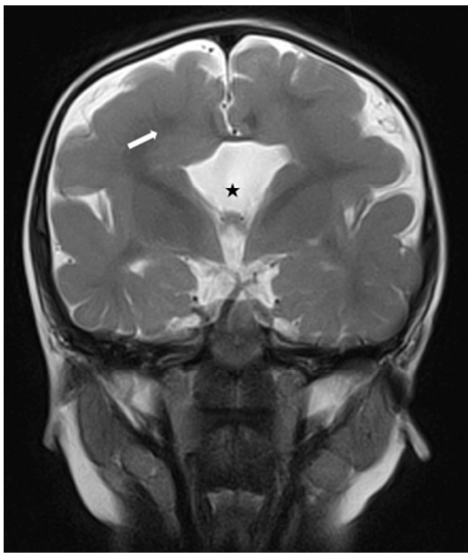

Figure 3. *Coronal T2 MRI image showing right frontal pachygyria (white arrow) with ipsilateral subcortical and subependymal cortical dysplasia. Similar cortical dysplasia is noted on the left to a lesser degree. Also noted is the absence of the septum pellucidum (black star).*

At 5 years of age the head circumference was 49 cm (10ile%) and he was hospitalized for status epilepticus. Susequent physical examinations remained unchanged except for hypersalivation, and being nonverbal.

3. Methods

Comparative genomic hybridization was performed using KaryoNIM 180K by Agilent Tech on blood samples from the patient and his parents which revealed a duplication at 3q25.1, (arr {hg19} 3q25.1 (150,771,625-151,094,167) x3) in the patient, and (arr {hg19} 3q25.1 (150,818,064-151,094,167) x3) in his father, who is neurologically asymptomatic.

4. Discussion

Upon query of ECARUCA, Decipher, and the Database of Genomic Variants, cases of duplication of variously sized portions of the long arm of chromosome 3 exist that either partially or completely overlap with the duplicated region identified in our patient [10-11]. Many of these cases derive from an asymptomatic parent with no maternal or paternal predominance. Some of these cases exist in association with abnormalities in neurogenesis, primarily microcephaly, or abnormalities in the development of the eyes/optic tracts and olfactory tracts [4, 12-15]. However, no pattern emerges in terms of a genotype/phenotype correlation from these cases probably due to their heterogeneity of location within this region of chromosome 3 and/or its combination with other CNV's. Of the 34 cases (including the present case) of pure 3q duplication identified, 14 report microcephaly and one each report absence of the corpus callosum, decreased white matter, and Dandy-Walker malformation with vermis hypoplasia, respectively, as cerebral findings (Table 1) [9, 6].

Table 1. *Variations in Neuroanatomy in Pure 3q Duplications involving 3q25.1 (Adapted from [9]) +, present; -, absent.*

Region of duplication of chromosome 3q	Schizencephaly	Microcephaly	Absence of Corpus Callosum	Decreased White Matter	Dandy-Walker Malformation / Vermis Hypoplasia	Citation
25.1	+	-	-	-	-	Present case
21-29	-	+	+	+	-	[9]
25-qter (4 cases)	-	+	-	-	-	[10]
24-26.31	-	+	-	-	-	[17]
21-27	-	-	-	-	+	[18]
25-28	-	-	-	-	-	[19]
23-27	-	+	-	-	-	[20]
21-27	-	+	-	-	-	[3]
25-29	-	+	-	-	-	[21]
25-29	-	+	-	-	-	[21]

This case is the first to report schizencephaly, an abnormality in neuronal organization which takes place late in the development of the brain, in association with any size duplication of the long arm of chromosome 3.

Jansen and Andermann in their review of polymicrogyria syndromes reported that sporadic and familial schizencephaly were thought to have been associated with mutations of the EMX2 gene located on chromosome 10q26.1, a gene known to be involved in brain segmentation in *Drosophila,* but was not found to be replicable, implicating more complex genetic regulation of this neurodevelopmental process [22]. In the same paper, bilateral frontoparietal polymicrogyria was implicated to be due to mutations in GPR56, a gene whose function is intimately involved in frontal lobe patterning of neuronal progenitor cells. Bae et al in 2014 showed that a 15-base pair mutation in this gene disrupts human cortical patterning around the Sylvian fissure via splice variation [23]. Of note, three genes which code for G-coupled proteins (GPR 171, GPR 87, GPR86) are contained in the duplicated region of our patient, expression profiles of which do not implicate postnatal function in the brain. This does not obviate these genes having a role in neuronal migration/organization early in human cerebral development.

Contained in the duplicated region of our patient is the gene CLRN1 (OMIM 606397), mutations of which are a known cause of retinitis pigmentosa 61 (OMIM 614180) and Usher

Syndrome Type 3A (OMIM 276902). Two genes in proximity to our patient's duplicated region are NLGN1 and ECT2, both of which reside in 3q26.31. NLGN1 codes for neuroligin-1, a protein that triggers presynaptic development [24]. ECT2 is a protein that is intimately involved in the development of the hippocampus and cerebellum [25].

5. Conclusion

Of the thirteen cases of pure duplication compiled, our patient's duplication is the smallest in size. The twelve other cases listed involve much larger duplications, and eleven of these involve larger morphogenic issues with brain development, seven of which being microcephaly. It is possible, given the above, that the long arm of chromosome 3 is intimately involved with many aspects of neurogenesis, and, depending on the size and location of the duplicated region (s), alterations in processes occurring earlier or later in this process may occur. Based on our patient, 3q25.1 may be a region involved late in this process.

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