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CASE REPORT

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Homozygous 15q13.3 microdeletion in a child with hypotonia and impaired vision: A new report and review of the literature

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Abstract

Although there are numerous reports of heterozygous 15q13.3 microdeletion, homozygous 15q13.3 microdeletion is rare. We report a new patient with homozygous microdeletion of 15q13.2q13.3 and review the previous literature reports. Common clinical features include encephalopathy, hypotonia, developmental delay, cortical vision impairment, optic nerve abnormality, epilepsy, and abnormal electroencephalogram (EEG) findings.

KEYWORDS

genetics, neurology, ophthalmology, pediatrics and adolescent medicine

1 | INTRODUCTION

Heterozygous 15q13.3 microdeletion syndrome is a clinical syndrome with high variability in expression and penetrance of symptoms.[1] Heterozygous 15q13.3 deletion is frequently inherited (reported as inherited in approximately 85.4% of individuals who have this deletion who have data available on inheritance in a review of large number of cases), but may also occur de novo.[2] Commonly reported associations include developmental delay or intellectual disability, epilepsy or seizures, speech problems, autism spectrum disorder, schizophrenia, mood disorders, and attention deficit hyperactivity disorder. Serious congenital anomalies are uncommon. A subset of individuals appears unaffected and is essentially healthy appearing neurotypical individuals. Some individuals have a mild phenotype with attention deficit disorder, learning disability or psychiatric or behavioral difficulties. More severely affected individuals may have autistic features or more severe cognitive impairment. Deletions in this region can vary in size, with the most typical size deletion approximately 1.5-2.0 Mb, approximately between 30.5 and 32.5 Mb, human genome build 19. Smaller deletions (<700 kb) and larger deletions (~3.9 Mb) can also occur.

Homozygous 15q13.3 deletion is a rare finding.[3-9] In contrast to individuals with the heterozygous deletion,

FIGURE 1 Facial appearance of proband

TABLE 1 Summary of clinical findings in known patients with homozygous 15q13.3 deletion

	Our patient	Masurel-Paulet et al 2010 & 2014[3,10] Patient 1	Masurel-Paulet et al 2014[10] Patient 2	Masurel-Paulet et al 2014[10] Patient 3	LePichon et al 2010[4]
Age	11 mo	9 y	4 y	30 mo	10 y
Sex	Female	Male	Male	Male	Male
Deletion size	2.0 Mb/2.0 Mb	1.5 Mb/1.5 Mb	1.5 Mb/1.5 Mb	1.5 Mb/1.5 Mb	1.5 Mb/1.5 Mb
Breakpoints	hg19 30 938 341-32 926 776	hg19 30 938 215-32 510 863	hg19 30 938 215-32 510 863	hg19 30 938 215-32 510 863	hg19 28 718 936-30 701 573
Inheritance	Biparental	Biparental	Biparental	Biparental	Biparental
Paternal phenotype	ADHD	Mild ID	No ID, but stopped school studies at 16		Healthy
Maternal phenotype	Healthy	Mild ID	No ID, but stopped school studies at 16		Healthy
Hypotonia	+	+	+	+	+
Developmental delay	+	+	+	+	+
Visual impairment	+	+	+	+	+
Abnormal optic nerve	+	+	+	+	+
ERG		Abnormal	Abnormal	Abnormal	
EEG	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Seizures	−	+ refractory	+ eye version and partial crises	+ absence and clonic	+ refractory
magnetic resonance imaging (MRI)	Delayed myelination at 4 mo	Retrocerebellar arachnoid cyst	Dysmorphic corpus callosum		

Note: Age indicates oldest age listed in clinical report.

Abbreviations: −, symptom absent; +, symptom present; ADHD, attention deficit hyperactivity disorder; Blank, data not available; hg18, Human Genome hg18 Build 36; hg19, human genome hg19 Build 37; ID, intellectual disability; Mo, months; y, years.

individuals with a homozygous 15q13.3 microdeletion consistently have shown a severe phenotype that includes encephalopathy, diffuse hypotonia, severe developmental delay, cortical vision impairment, and epilepsy or abnormal EEG. Although the number of affected patients reported with homozygous 15q13 microdeletion is small, the features have been highly consistent among the known patients. We report here an additional patient with homozygous 15q13.3 microdeletion to provide further information and discussion of this rare syndrome.

2 | CASE PRESENTATION

Our patient was initially evaluated in neurology clinic due to concerns of hypotonia and developmental delay. She was the

Endris et al 2011[5] Patient 1	Endris et al 2011[5] Patient 2	Spielmann et al 2011[6] Patient 1	Spielmann et al 2011[6] Patient 2	Liao et al 2011[7]	Hoppman-Chaney et al 2013[8]	Prasun et al 2014[9]
Deceased at 13 y	20 mo	10 y	9 y	6 y	4 y	23 mo
Male	Male	Male	Female	Female	Male	Female
1.5 Mb/680 kb	1.5 Mb/3.4 Mb	1.5 Mb/1.5 Mb	1.5 Mb/1.5 Mb	410 kb/410 kb	CHRNA7/ CHRNA7	1.28 Mb/410 Kb
	hg18 Heterozygously deleted region: min 26 884 685-28 877 426; Homozygously deleted region: min 28 891 708-30 298 296	hg19 28 758 622-30 226 376	Presumed the same as sibling, tested by FISH	hg19 29 816 893-30 226 405		
Biparental	Biparental	Maternally inherited; father not tested		Biparental inheritance	Not tested	Not tested
Healthy	Healthy	Not reported		Learning disability	Unknown	ADHD
Healthy	Healthy	Mild ID, learning difficulties and abnormal electroencephalogram (EEG) findings, no history of seizure		No neurologic symptoms	Unknown	Healthy
+	+	+	+	+	+	+
+	+	+	+	+	+	+ started rolling at 8 m
+	+	+	+	+		+
−	+	−	−			
		Abnormal	Abnormal			normal
Abnormal	Abnormal	Abnormal	Abnormal	abnormal		normal
+ refractory focal, later generalized seizures	+ complex partial seizures	+ refractory		+ absence	−	
Reduced volume of frontal lobe, dilated extraaxial spaces	Abnormal signal WM, enlarged LV dysplastic cerebellum	Subarachnoid cysts and frontal supratentorial atrophy at 3 y	Multiple subarachnoid cysts	Normal at 6 mo	Structural brain anomaly	Normal at 3 mo

product of her mother's second pregnancy. Maternal age was 24 years, and paternal age was 21 years. She had a generally healthy 5-year-old maternal half-sister with normal development and normal developmental milestones. Her father reported a history of attention deficit hyperactivity disorder. Her mother was in generally good health with no clinical or developmental concerns. The pregnancy was uncomplicated until around 36 weeks gestation when there was concern of decreased rate of head growth on ultrasound. Delivery was by induced vaginal delivery at 41 weeks gestational age. Birth weight was 6 pounds and 10 ounces, and birth length was 20-1/2 inches.

Our patient had long eyelashes, epicanthal folds, and mildly anteverted nares but was not significantly dysmorphic. (See photo of proband in Figure 1). On neurologic exam, pupils were isocoric and reactive to light. She did not appear to be able to fix or track objects or faces. Eye movements were

conjugate but frequently roving with intermittent upward rolling. In the first few months of life she also had occasional brief horizontal pendular nystagmoid intrusions. Motor exam was notable for prominent diffuse hypotonia, with low muscle bulk throughout, but no clear wasting or weakness. Muscle stretch reflexes were absent at the biceps and 1:4 at the quadriceps. Formal ophthalmology exam at 5 months of age showed optic nerve hypoplasia and delayed visual maturation.

Magnetic resonance imaging (MRI) of the brain showed normal structure and volume, with mildly delayed myelination for age. EEG revealed prominent and nearly continuous high-amplitude occipital slowing (2-4hertzwhenawake, 1-3hertzwhenasleep), usually bilateral and synchronous, but intermittently asymmetric without a clear predilection for one hemisphere over the other. Intermittent focal spike waves were observed as well. At 7 months old these appeared over the right occipital region but also less frequently independently over the left occipital. At 11 months old intermittent spike waves were less frequent and seen primarily over the bilateral paracentral region, often synchronous or with shifting laterality. Cardiology evaluation revealed a normal electrocardiogram and echocardiogram. Aberrant right subclavian artery was detected by MRI.

Her serious clinical concerns prompted further diagnostic work-up. Clinical SNP whole-genome array revealed two alterations: a homozygous copy number loss of 2.0 Mb at 15q13.2q13.3 (30 938 341-32 926 776) and small single copy number gain of 122 Kb on 9q34.3 (137 595 462-137 717 991).

Parental studies were undertaken to determine if the imbalances were de novo or inherited. Parental SNP whole-genome array revealed both parents carried identical heterozygous deletions at 15q13.2q13.3. There was no known consanguinity. Clinical testing was deferred until a later age for her half-sister as she had no clinical or developmental concerns at the time of evaluation.

The family had another pregnancy after the diagnosis of the proband. They elected to undergo amniocentesis with SNP whole-genome array, which revealed an unaffected fetus with normal copy number at 15q13.3.

2.1 | Diagnostic investigation

A whole-genome array of genomic DNA was performed on the proband and her parents (CombiMatrix, Irvine) using a custom-designed Illumina single-nucleotide polymorphism (SNP) array (Illumina) with >845 000 SNP markers covering both coding and noncoding human genomic sequences. This revealed two alterations on the proband's genome: a homozygous copy number loss of 2.0 Mb at 15q13.2q13.3 (30 938 341-32 926 776) and small single copy number gain of 122 Kb on 9q34.3 (137 595 462-137 717 991). The minimum/maximum genomic coordinates for the deletion on 15q13.2q13.3 fall between 30 928 895-32 522 589 (minimum) and 30 385 284-32 922 385 (maximum). Genomic imbalances are reported using UCSC human genome build 19 (NCBI build 37, Feb 2009). Genes within the deletion at 15q13.2q13.3 included *LOC100288637, HERC2P10, FAN1, MTMR10, MIR211, TRPM1, LOC102725022, LOC283710, KLF13, OTUD7A, CHRNA7, GOLGA8K, ULK4P3, ULK4P1, ULK4P2, GOLGA8O, WHAMMP1, LOC100996255, GOLGA8N, LOC101928042*, and *ARHGAP11A*. The duplication at 9q34.3 partially overlapped the gene *COL5A1*.

3 | DISCUSSION

Only a small number of patients with homozygous 15q13.3 deletion are reported so far in the clinical literature. Despite the small number, the clinical phenotype has been consistent. A clear phenotype of encephalopathy, hypotonia, developmental delay, cortical vision impairment, epilepsy, and abnormal EEG findings has emerged. See Table 1 for a comparison of features in our patient and previously reported patients.

The small duplication at 9q34.3 was paternally inherited. This duplication partially overlapped the gene *COL5A1*. We suspected this duplication to be more likely benign and did not anticipate a partial duplication of *COL5A1* to have significant clinical consequence unless it was in a region disruptive to another allele or gene.

These patients have helped spur discussion of which genes may underlie the key features of this phenotype. They may also help bring greater understanding of the roles of these genes in the heterozygous phenotype as well. Two key genes involved in the phenotype appear to be *CHRNA7* (Cholinergic Receptor, Neuronal Nictonic, Alpha Polypeptide 7) and *TRPM1* (Transient Receptor Potential Cation Channel, Subfamily M, Member 1).[8]

It has been posited that in the heterozygous deletion, the variability in the phenotype may depend on variation in the remaining allele of key genes such as *CHRNA7*. The severe phenotype when there is no second allele of *CHRNA7* appears supportive of this hypothesis. However, Masurel-Paulet et al sequenced *CHRNA7* in a cohort of individuals with heterozygous 15q13.3 deletion and found no sequence variants to explain the variability in phenotype.[3] Of course, other variations among the other approximately 20 000 genes in the genome may also play compensatory roles. Elucidating potential key players may be inherently difficult, though candidates may be found as the pathways and interactions become clearer. LePichon et al, pursued a genome-wide gene expression approach in their patient with homozygous 15q13.3 deletion, suggesting a downstream effect of loss of *CHRNA7* modulation of TNFα may play a role in the phenotype.

TRPM1 has been nominated as playing a role in the ophthalmologic findings.[10] Alterations in the gene *TRPM1* are known to cause autosomal recessive congenital stationary

night blindness. TRPM1 channel opening is essential for rod bipolar pathway establishment in development, making it a plausible initial candidate.[11] Mausurel-Paulet et al noted that among the patients with smaller homozygous deletions that did not include *TRPM1*, the visual component of the phenotype was absent. Our patient's deletion includes *TRPM1*, and she has clear ophthalmologic findings including optic nerve pallor and cortical vision impairment. However, patients who have a deletion that does not include *TRPM1* have been reported to have other visual concerns such as difficulty with visual tracking. *TRPM1* may play a role at the level of the retina and the optic nerve, but it is possible *CHRNA7* may play a role at the cortical level.

Additionally, we noted that this case further supports the use of chromosome microarray in the initial steps of genetic work-up of children with profound neurological symptoms.[12] Assessment of chromosome copy number variants is an important initial step in the genetic evaluation and should be considered early in the genetic evaluation process. Not only does this provide an opportunity for better prognosis and management decisions, it also allows for family planning and evaluation decisions for the patient's family and their relatives. The information regarding recurrence risk and early testing was valuable for our patient whose parents were still in the active family planning stage. It will provide testing options to determine recurrence risks for her sister when she is of family planning age.

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CONFLICT OF INTEREST

None reported.

AUTHOR CONTRIBUTIONS

JS, KS, RF, and ALY drafted and edited manuscript. JM wrote the description of neurological exam. ALY coordinated the group and oversaw drafting, editing and responded to reviewer comments.

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