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De Novo Interstitial Deletion of 9q in a Pediatric Patient With Global Developmental Delay

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Abstract

Cytogenomic microarray (CMA) methodologies, including array comparative genomic hybridization (aCGH) and single-nucleotide polymorphism-detecting arrays (SNP-array), are recommended as the first-tier test for the evaluation of imbalances associated with intellectual disability, autism, and multiple congenital anomalies. The authors report on a child with global developmental delay (GDD) and a *de novo* interstitial 7.0 Mb deletion of 9q21.33q22.31 detected by aCGH. The patient that the authors report here is noteworthy in that she presented with GDD and her interstitial deletion is not inclusive of the 9q22.32 locus that includes the *PTCH1* gene, which is implicated in Gorlin syndrome, or basal cell nevus syndrome (BCNS), has not been previously reported among patients with a similar or smaller size of the deletion in this locus suggesting that the genomic contents in the identified deletion on 9q21.33q22.31 is critical for the phenotype.

Keywords

behavior, children, developmental delay, developmental disability, genetics, infant, intellectual disability, mutation, neonate, pediatric

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Global developmental delay (GDD) is a subset of developmental disabilities defined as significant delay in 2 or more developmental components, including gross/fine motor, speech/language, cognition, social/personal, and activities of daily living.[1] Significant delay is specifically defined as performance 2 standard deviations or greater below the mean on standardized testing compared to peers of the same age. Global developmental delay affects approximately 1%–3% of children, highlighting the necessity to determine specific causes for it.

Current American Academy of Neurology (AAN) and Child Neurology Society (CNS) guidelines[2] for the evaluation of children with GDD begin with obtaining a detailed history, an electroencephalogram (EEG) test, metabolic studies, and T4 levels if the universal newborn screening was not done, screening for autism or language disorders, and referring to audiology and ophthalmology screening. Further studies include brain magnetic resonance imaging (MRI), lead screen, cytogenetic screen, fragile X screen, metabolic testing, subtelomeric rearrangement testing, Rett syndrome testing, and genetics consultation. Importantly, clinical experience and analytical reasoning guide the decisions to pursue appropriate and relevant testing.

While GDD is one of the most common reasons for referral to a pediatric neurologist, many cases of GDD do not have definitive etiologic diagnoses because of a lack of imaging

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abnormalities, a normal metabolic screen, and an unremarkable medical and family history.[3] The advent of cytogenetic and molecular studies has drastically improved our ability to determine specific diagnoses in cases of GDD, leaving only a minority of children with undetermined etiologies of GDD.[4] Accurate etiologic determination of GDD has specific implications regarding treatment, prognosis, management of any associated conditions, and prevention.[1] As with many other chronic illnesses, determining the specific cause helps empower the family to advocate for the child, plan for the child's future, and limit further unnecessary testing.

Patient Description

This female child was initially referred to our pediatric neurology clinic at 12 months of age for evaluation of GDD.

Birth and Neonatal History

The patient had an unremarkable vaginal delivery at term to a gravida 2, para 1, 36-year-old mother with a birth weight of 3402 g. There were no complications with pregnancy or delivery. She was found to have a small atrial septal defect (ASD) and physiologic pulmonary stenosis (PPS) at 2 months of age, deemed insignificant for that age. By 8 months of age, the ASD had spontaneously closed. At that time, she was noted to have an unremarkable physical examination and has been thriving at home, feeding without difficulty, gaining weight, and developing appropriately.

Developmental Delay

Her motor development was delayed. Her mother first became concerned about her development at 5 months of age because she was not supporting her weight when sitting, and this continued until 12 months of age. At 11 months of age, she was diagnosed with hypotonia and qualified for physical therapy and occupational therapy. She began rolling over at 14 months and crawling at 17 months. At 19 months, she was able to pull herself up to stand and required holding on to maintain her stance.

Her language development was also delayed. At 12 months, she followed simple directions such as "no," clap her hands, and touch her nose. She was able to call her dad specifically but did not speak other words. She did not wave goodbye. At 14 months, she was able to say "hi," "bye," and "dada." At 19 months, she had a vocabulary of about 10 words.

The family history was unremarkable. Her elder sister, who was 4 years old, had no developmental issues.

Neurologic Evaluation

During her initial neurology evaluation at 12 months of age, head circumference was 47 cm, 91st percentile, weight in the 89th percentile, and a height in the 64th percentile. Her father, mother, and 4-year-old elder sister's head circumferences are in the 98th, 90th, and 75th percentiles, respectively. Thus, her head circumference can be proportional to her other growth parameters and might be familial. Her physical examination at that time revealed intermittent bilateral exotropia, which had been witnessed since the age of 7 months. She pulled to sit well, did not roll over, did not crawl, and did not extend her lower extremities in an attempt to stand. Otherwise, she had a nonfocal examination. The parents denied developmental regression and denied any seizure episodes, although noted that the child had 3 episodes of "eye rolling" during bowel movements.

Further Workup

An EEG test at that time was normal. A brain MRI at 13 months showed an incidental calvarian dermoid cyst within the left subcutaneous tissues of the level of C1 to C2 but was otherwise unremarkable. Metabolic workup was negative.

An ophthalmology evaluation determined that her exotropia would be corrected with glasses and that she has bilateral refractive amblyopia secondary to astigmatism. An otolaryngology evaluation revealed that the patient has ankyloglossia, a congenital anomaly characterized by a short frenulum.

Genetic Testing

The patient was evaluated by a medical geneticist at 14 months of age, and CMA testing was ordered to rule out unbalanced structural and numerical chromosomal abnormalities. Cytogenomic microarray testing using the SurePrint G3 ISCA CGH+SNP 4x180 k microarray (Agilent Technologies, Santa Clara, CA)[5,6] led to the identification of a heterozygous 7.0-Mb deletion of chromosome 9q21.33q22.31 (chr9:87,331,806-94,336,693) (Figure 1). The deletion included 45 genes and transcripts and had only minimal overlap with copy number variants (CNVs) reported among healthy individuals in the Database of Genomic Variants (DGV; http://dgv.tcag.ca) (Figure 2).[7] The interstitial 9q21.33q22.31 deletion was confirmed by fluorescence in situ hybridization (FISH) in all interphase nuclei using a bacterial artificial chromosome (BAC) probe that hybridized to the 9q21.33 region and a control probe specific to the subtelomeric region of chromosome 9q (Figure 3). Subsequent parental CMA testing determined that the 7.0-Mb interstitial deletion was not inherited and, therefore, occurred de novo in this patient (Figure 4). The family declined further testing with whole exome sequencing (WES) or targeted gene panels.

Continued Care

The patient continued to have a nonfocal neurologic examination at 19 months. At 25 months of age, the patient underwent an elective excision of the calvarian lesion, with an uneventful surgery and recovery.

Discussion

Interstitial deletions of chromosome 9q are rare and are characterized with multiple congenital anomalies, dysmorphic

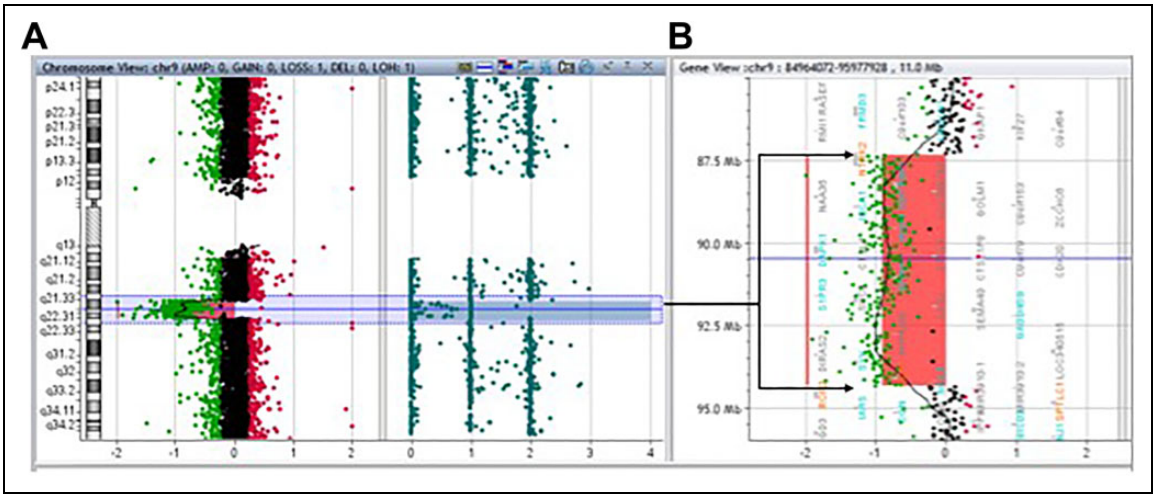

Figure 1. (A) Location of the deletion within banding region 9q21.33q22.31 and (B) close view shows a 7.0-Mb deletion overlaid on the raw log2 probe plot. Chromosomal microarray analysis was performed using array comparative genomic hybridization (aCGH) with Agilent's SurePrint G3 4x180 k CGH+ single-nucleotide polymorphism (SNP). Array CGH data were analyzed using Cytogenomics (v.3.0.2.11, Agilent) and Bench LAB CNV (v5.1.1, Cartagenia).

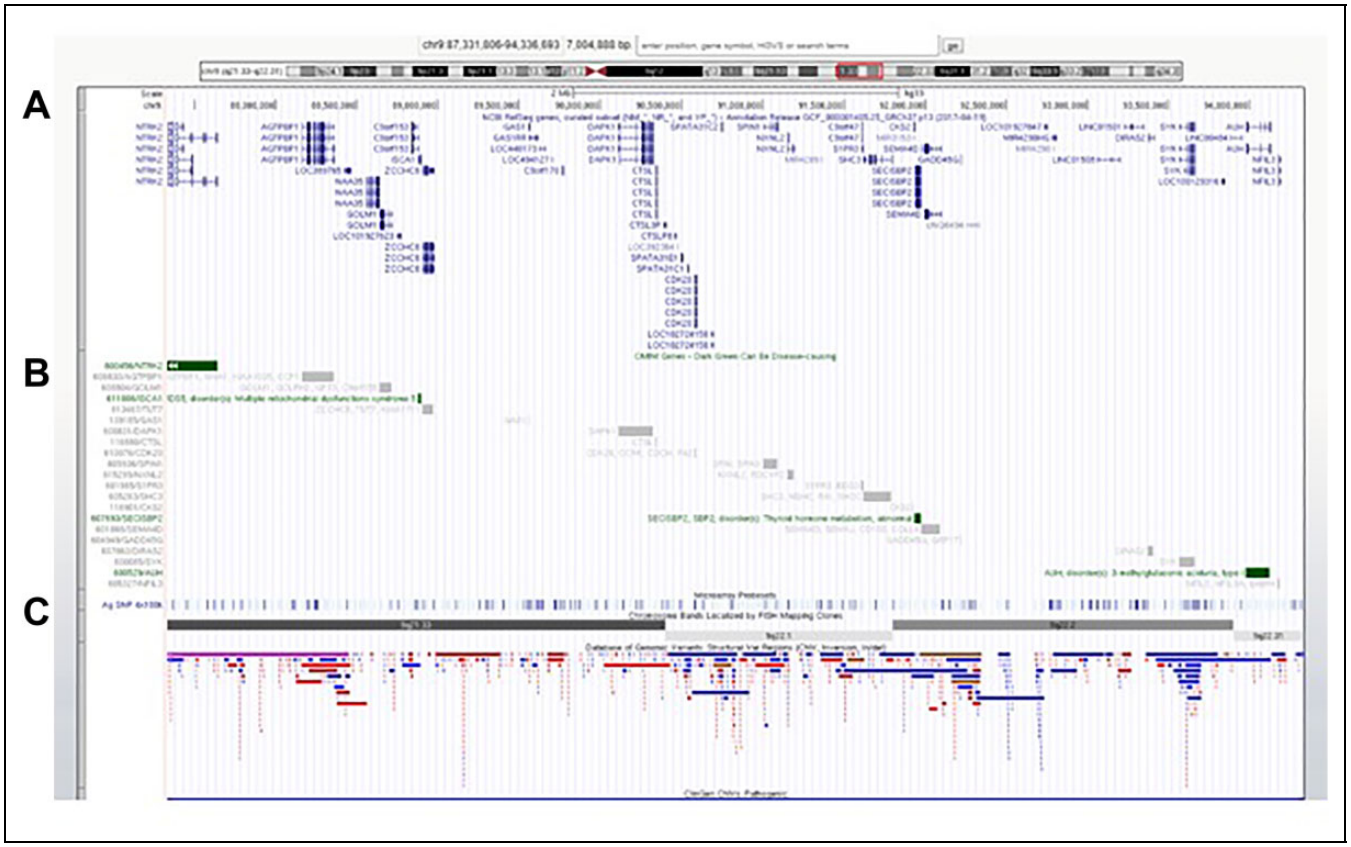

Figure 2. The size, extent, and genomic content of the deletion in this patient. Genomic coordinates from array comparative genomic hybridization (aCGH, chr9:87,331,806-94,336,693 [hg19]) were analyzed on UCSC genome browser. UCSC genome browser tracks (hg19) showing (A) all genes (RefSeq) (B) OMIM genes (green bars) (C) Database of Genomic Variants (DGV).

features, developmental delay, and intellectual disability. The specific deletion detected in our patient includes over 45 genes and transcripts, among them 3 previously reported Mendelian disease genes (*NTRK2, SECISBP2*, and *AUH*). Mutations in *NTRK2* are associated with a condition involving mood disorders, Alzheimer disease, autism, and developmental delays.

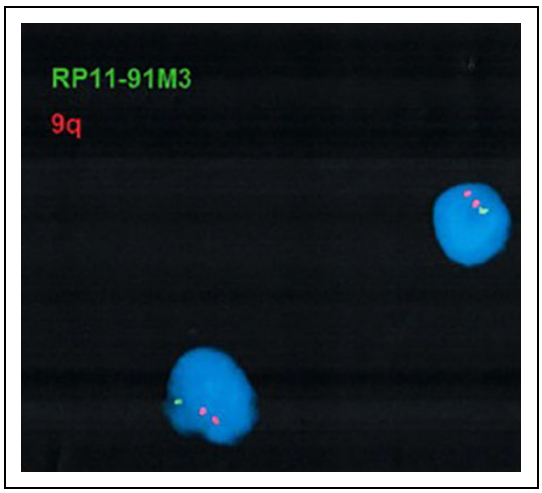

Figure 3. The identified deletion was confirmed by fluorescence in situ hybridization (FISH) using a bacterial artificial chromosome (BAC) probe targeted to the 9q21.33 region (RP11- 91M3, Empire Genomics) and a control probe specific to the subtelomeric region of chromosome 9q (TelVysion 9q, D9S325, Abbott Molecular). Loss of the green fluorescent hybridization signal confirmed the deletion in the nuclei. Chromosomes were stained with DAPI.

Mutations in the *SECIBP2* and *AUH* genes are associated with autosomal recessive conditions: an abnormal thyroid metabolism disorder and type 1 methylglutaconic aciduria, respectively.[8–10]

The *NTRK2* (neurotrophic receptor tyrosine kinase 2) gene localizes to chromosome 9q21.33 and contains 23 exons. *NTRK2* encodes TrkB, a membrane receptor kinase that autophosphorylates through the MAPK signaling pathway when activated by neurotrophin binding.[11] Gene variants involving the *NTRK2* gene are associated with a number of neurological and psychiatric disorders such as mood disorders,[12] vulnerability to nicotine or alcohol dependence,[13,14] Alzheimer disease,[15,16] and autism.[17]

The *SECISBP2* (selenocysteine insertion sequence-binding protein 2) gene, also known as *SBP2*, localizes to chromosome 9q22.2. The mutation of this gene leads to defects in incorporation of selenocysteine and, as a result, leads to reduced synthesis of most of the 25 known human selenoproteins.[18] Deficiencies in selenoproteins have been implicated in azoospermia, axial muscular dystrophy, photosensitivity, immunodeficiencies, and abnormal thyroid function.[18,19]

The *AUH* (AU RNA binding methylglutaconyl-CoA hydratase) gene localizes to chromosome 9q22.31. Mutations in this gene are implicated in 3-methylglutaconic aciduria type I, an autosomal recessive disorder of leucine degradation.[20] Speech delay and GDD are often prominent symptoms of the resulting disease.[20,21]

To elucidate the clinical significance of the identified deletion, the authors reviewed published case reports in the literature and evaluated the phenotypes. Table 1 presents the published loci overlapping with that of the current study. Twenty-eight cases of interstitial 9q deletions were found span, flanked, or partially overlapped with the current case's deletion.[8–10,22–34] The clinical features of individuals with deletion of 9q varied with few common features.

Gorlin syndrome, also known as the nevoid basal cell carcinoma syndrome (NBCCS) or basal cell nevus syndrome (BCNS), is a disorder involving the *PTCH1* gene found on 9q22.32.[28] *PTCH1* was not implicated in this study because the deletion found was 9q21.33q22.31, and therefore did not involve 9q22.32. However, much of the literature involving 9q interstitial deletions involves the Gorlin syndrome. It has been proposed that the diagnosis of Gorlin syndrome can be made by

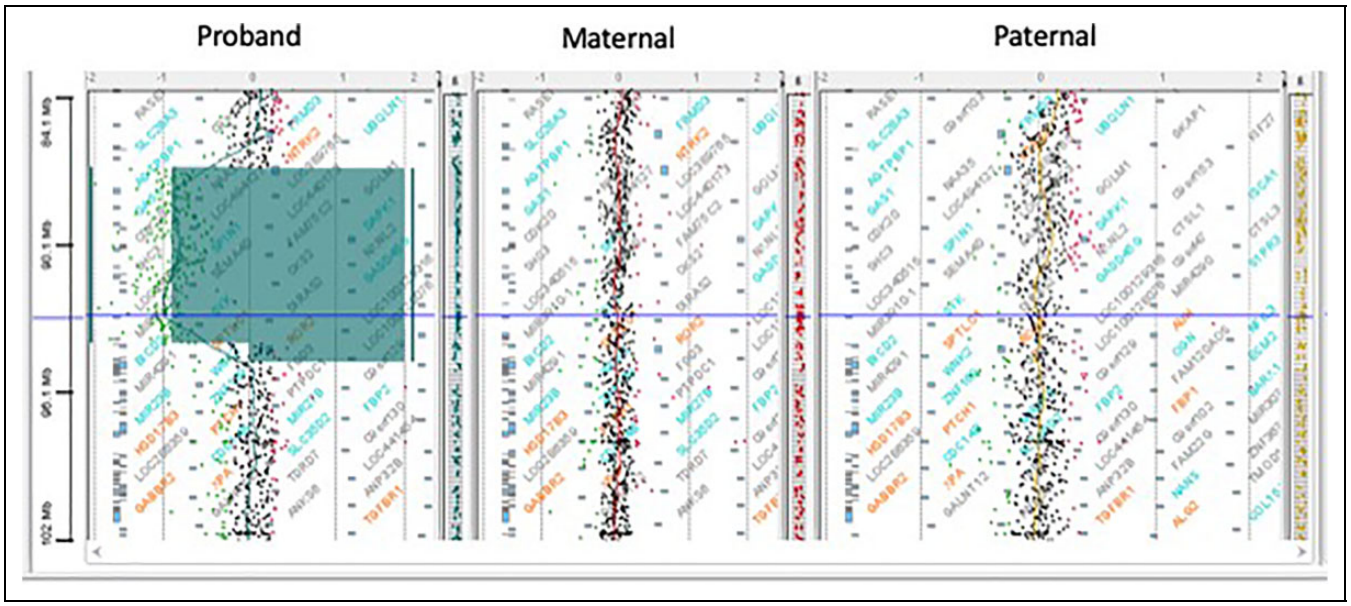

Figure 4. Parental analysis by array comparative genomic hybridization (aCGH) showed that neither parent was a carrier of this aberration, indicating that the deletion occurred de novo in the proband.

Table 1. Published case reports in the literature of loci overlapping with that of the current study.

Source	Current study	Zhang et al. 2015	Reichert et al. 2015	Pua et al. 2014	Garavelli et al. 2013	Isidor et al. 2013	
						Patient 1	Patient 2
Inheritance	De novo	?	De novo	De novo	De novo	De novo	De novo
Position (Mb)	9q21.33q22.31	Discontinuous 9q21.33-9q22.33	9q22.31q22.32	9q21.32q21.33	9q22.2q31.1	9q22.3	9q22.3
Deletion size (Mb)	7.0	Variable	3.99	2.6	10.9	1.7-8.9	1.7-8.9
OMIM disease genes	NTRK2, SECISBP2, AUH	PTCH1, NTRK2, SECISBP2, AUH, FBP1, HSD17B3	PTCH1, FANCC	NKGD2, KIF27, UBQLN1, HNRNPK, RMI1, NTRK2	PTCH1, FANCC	PTCH1	PTCH1
Gorlin syndrome	−	−	−	−	+	+	+
Cardiac tumors	−	+	−	−	−	−	−
Developmental delay	+	−	−	−	+	+	+
Hydrocephalus	−	−	−	−	+	−	−
Metopic fusion	−	−	+	−	−	−	−
Macrosomia	−	−	+	−	−	−	−
Macrocephaly	−	−	−	−	−	−	−
Hearing Loss	−	−	−	−	−	−	−
Atrial septal defect	+	−	−	+	−	−	−
Epilepsy	−	−	−	−	−	−	−
Strabismus	+	−	−	−	−	−	−
Pulmonary stenosis	+	−	−	−	−	−	−
Failure to thrive	−	−	−	−	−	−	−
Recurrent infection	−	−	−	+	−	−	−
Other	Calvarian cyst, ankyloglossia, hypotonia		Ventriculomegaly	Craniofacial abnormalities, bicornuate uterus, bilateral hip dislocation, hypotonia	Wilms tumor, multiple tumors	Long and thin fingers, dolichocephaly	Wilms tumor, macroglossia

Source	Siggberg et al. 2011	Mosterd et al. 2009	Yamamoto et al. 2009		Nowakowska et al. 2007	Cajaiba et al. 2006
			Patient 1	Patient 2		
Inheritance	De novo	De novo	De novo	De novo	?	?
Position (Mb)	9q22.2q22.32	9q22	9q21.33q22.33	9q21.33q31.1	9q22.1q22.32	9q22q32
Deletion size (Mb)	5.3	11.24	15.33-16.04	18.08-18.54	7.7	?
OMIM disease genes	ROR2, SYK	PTCH1, FANCC, XPA	PTCH1	PTCH1	PTCH1, ROR2	PTCH1
Gorlin syndrome	−	+	+	+	+	+
Cardiac tumors	−	−	−	−	−	−
Developmental delay	−	−	+	−	−	−
Hydrocephalus	−	−	−	−	−	−
Metopic fusion	−	−	−	+	−	−
Macrosomia	−	−	+	+	−	−
Macrocephaly	−	−	−	+	−	−
Hearing Loss	−	−	−	−	−	−
Atrial septal defect	−	−	−	−	−	−
Epilepsy	−	−	+	+	−	−
Strabismus	−	−	+	−	−	−
Pulmonary stenosis	−	−	−	−	+	−
Failure to thrive	−	−	+	−	−	−
Recurrent infection	+	−	−	−	−	−
Other	Craniofacial abnormalities, dysarthria		Overfriendliness, attention deficit, ventriculomegaly, ganglioglioma	Craniofacial abnormalities, overfriendliness, attention deficit and hyperactivity, retinal detachment, cataract, glaucoma, functional thyroid tumor, craniosynostosis, double urethra	Hypoplastic clavicles, craniofacial abnormalities	Rhabdomyosarcoma, Wilms tumor, macroglossia

(continued)

meeting 2 major criteria and 1 minor criteria or 1 major criteria and 3 minor criteria.[35] The major criteria include lamellar calcification of the falx, jaw keratocysts, palmar/plantar pits, multiple basal cell carcinomas (>5 in a lifetime or one before the age of 30 years), and first-degree relatives with Gorlin syndrome.[35] The minor criteria include child medulloblastomas, lympho-mesenteric or pleural cysts, macrocephaly, cleft lip/palate, vertebral/rib anomalies, preaxial or postaxial polydactyly, ovarian/cardiac fibromas, and ocular anomalies.[35] Other features that are not typically associated with Gorlin syndrome, such as metopic craniosynostosis, hydrocephalus, macrosomia, and developmental delay, were seen in high frequencies in cases with confirmed pathogenic variants of *PTCH1*.[33] The patient involved in this study did not meet any of the major or minor criteria as anticipated by the lack of involvement of 9q22.32 and *PTCH1*.

Our patient has a complex phenotype consisting of GDD, exotropia, ankyloglossia, and a calvarian dermoid cyst. Heretofore, her clinical presentation is less severe than those documented in cases with CNVs of the aforementioned genes that are affected by her interstitial deletion. Therefore, it appears that this patient's clinical synopsis is not predicted simply by the roles of each of the genes involved in this novel interstitial deletion.

Table 1. (continued)

Source	Chen et al. 2006	Chen et al. 2005	Boonen et al. 2005	L'Hermine et al. 2002	Shimkets et al. 1996 Patient 1	Shimkets et al. 1996 Patient 2
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo
Position (Mb)	9q22.3q31.3	9q21.1q22.2	9q21.3q31	9q22.2q31.1	9q22	9q22q32
Deletion size (Mb)	12	?	15	?	10-16 cM	22-39 cM
OMIM disease genes	PTCH1	?	PTCH1, ROR2	?	PTCH1	PTCH1
Gorlin syndrome	+	–	+	–	+	+
Cardiac tumors	–	–	–	–	–	–
Developmental delay	–	–	+	–	–	–
Hydrocephalus	–	–	–	–	+	–
Metopic fusion	–	–	–	–	–	–
Macrosomia	+	–	–	–	–	–
Macrocephaly	+	–	–	–	+	–
Hearing Loss	–	–	–	–	+	+
Atrial septal defect	–	–	–	–	–	–
Epilepsy	–	–	–	–	–	–
Strabismus	–	–	+	–	–	–
Pulmonary stenosis	–	–	+	–	–	–
Failure to thrive	–	–	+	–	–	+
Recurrent infection	–	–	+	–	–	–
Other		Craniofacial abnormalities, thick nuchal fold	Epicanthic folds, abnormal palmar crease, bilateral testes retention, bilateral postaxial polydactilia pedes, excess nuchal skin, craniofacial abnormalities, ventriculomegaly, bilateral inguinal hernias	IUGR, female pseudohermaphroditism, craniofacial abnormalities	Bilateral inguinal hernias, growth delay, corpus collosum agenesis	Congenital anomalies of the great vessels

Source	Muller et al. 2012 Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo
Position (Mb)	9q22.3	9q22.3	9q22.3	9q22.3	9q22.3	9q22.3	9q22.3	9q22.3	9q22.3	9q22.3
Deletion size (Mb)	20.5	10.85	9.85	8.28	8.07	4.5	2.03	1.84	1.08	0.352
OMIM disease genes	PTCH1	PTCH1	PTCH1	PTCH1	PTCH1	PTCH1	PTCH1	PTCH1	PTCH1	PTCH1
Gorlin syndrome	+	+	+	+	+	+	+	+	+	+
Cardiac tumors	–	–		–	–	–	–	–	–	–
Developmental delay	–	+	+	+	+	+	+	+	+	+
Hydrocephalus	–	+	+	+	+	–	–	–	+	–
Metopic fusion	+	–	–	–	+	–	+	+	–	–
Macrosomia	–	–	–	–	–	–	±	+	–	–
Macrocephaly	–	–	–	–	–	–	–	–	–	–
Hearing Loss	–	–	–	–	–	–	–	–	–	–
Atrial septal defect	–	–	–	–	–	–	–	–	–	–
Epilepsy	–	–	–	–	–	–	–	–	–	–
Strabismus	–	–	–	–	–	–	–	–	–	–
Pulmonary stenosis	–	–	–	–	–	–	–	–	–	–
Failure to thrive	–	–	–	–	–	–	–	–	–	–
Recurrent infection	–	–	–	–	–	–	–	–	–	–
Other										

In conclusion, the authors present a unique case of a 7.0-Mb 9q interstitial deletion at 9q21.33q22.31 in a patient who presented with GDD. Of note, there are very few cases of overlapping deletions that do not fit criteria for Gorlin syndrome. As there are not many reports of deletions spanning the segment 9q21.33q22.31 in the literature, follow-up would be invaluable in order to extend existing knowledge of this disease course and progression. Future reports of gene deletions in the 9q21.33q22.31 segment would also be beneficial in helping elucidate the disease progression and the biological mechanisms that are present.

Author Contribution

Mr. Keselman collected the data and drafted the manuscript. Dr Singh analyzed and interpreted the CMA and FISH data and revised the manuscript. Dr Cohen analyzed and interpreted the CMA and FISH data, revised the manuscript, and oversaw the case report. Dr Fefer performed the clinical evaluations, interpreted the data, drafted and revised the manuscript, and oversaw the case report. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Declaration of Conflicting Interests

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Ethics Approval

Written informed consent for patient information and images to be published was provided by the patient's parents.

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