CASE REPORT

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A 9.8 Mb deletion at 7q31.2q31.31 downstream of *FOXP2* in an individual with speech and language impairment suggests a possible positional effect

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Abstract

Haploinsufficiency of *FOXP2* causes *FOXP2*-related speech and language disorder. We report a 9.8 Mb deletion downstream of *FOXP2* in a girl with speech and language impairment, developmental delay, and other features. We propose involvement of *FOXP2* in pathogenesis of these phenotypes, likely due to positional effects on the gene.

KEYWORDS
7q31, CMA, deletion, *FOXP2*, language, positional effect, speech

1 | INTRODUCTION

Deletions localized to chromosome region 7q31 have been found in individuals with neurodevelopmental disorders characterized by delayed speech and language impairment. The majority of the deletions include the forkhead box P2 (*FOXP2*) gene, a transcription factor that is highly expressed in the brain and essential for proper brain development and function.[1] Disruption of the gene causes autosomal dominant *FOXP2*-related speech-language disorder 1 (SPCH1; OMIM 602081) with core features of childhood speech apraxia and orofacial dyspraxia.[2] Affected individuals may also have dysarthria, moderate to severe receptive and expressive language disorder, and reading and spelling impairments. In addition to speech- and language-related phenotypes, a broad spectrum of clinical manifestations such as mild motor delay, mild cognitive impairment, behavioral anomalies, and mild facial dysmorphism have been reported in affected individuals with variants in *FOXP2*.[3] Causative genetic alterations of *FOXP2* include missense, frameshift, and nonsense variants, intragenic deletions, whole gene deletions, translocations, inversions interrupting the reading frame, and maternal uniparental disomy for chromosome 7.[3-14] Furthermore, several recent reports describe patients with language and speech disorders in whom structural variants or deletions were identified that do not interrupt the coding region of the *FOXP2* gene itself, but perturb nearby genomic regions. It has been hypothesized that these structural abnormalities

and deletions affect non-coding regulatory elements of the gene.[1,15,16,17,18]

Recently, a heterozygous 4.7 Mb deletion at 7q31.2q31.31 that is located 600 kb downstream of the *FOXP2* gene was identified in three family members with speech, language, and neurodevelopmental phenotypes including microcephaly. The 15 protein-coding genes included in the deletion have no known implications in language disorder, and phenotypes of the affected individuals overlapped highly with those in *FOXP2*-related language and speech disorder, suggesting the involvement of *FOXP2* in pathogenesis, likely due to positional effects on the gene.[19] Here, we report a 6-year-old girl with language impairment, global developmental delay, relative microcephaly, attention deficit/hyperactivity disorder (ADHD), and learning difficulties with a heterozygous 9.8 Mb deletion at 7q31.2-q31.33 that is located 550 kb downstream of the *FOXP2* gene. The deletion was inherited from her father, who also has a history of abnormal speech and learning disabilities.

2 | CLINICAL REPORT

The proband is a 6-year-old female who was born to nonconsanguineous parents. She was delivered at 37 weeks gestational age with a birth weight of 3.77 kg (74th percentile) and head circumference of 33.5 cm (22nd percentile). Pregnancy, labor, and delivery were complicated by maternal treatment with ziprasidone (Geodon®, Pfizer) and metformin as well as exenatide (Byetta®, Amylin). She had a low heart rate and was noted to have extra cartilage on her ear, which has been surgically removed.

She initially presented for evaluation at 10 months of age due to microcephaly. On examination, her weight was 6.975 kg (0.5 percentile); her height was 64.3 cm (0.4 percentile), and her head circumference was 41 cm (0.1 percentile). She was proportionally small. According to her medical records, her head circumference had fallen below the second percentile for age by 2 months and persisted on a curve paralleling the normal curve until at least 18 months of age. An MRI scan of her brain and spine showed a Chiari malformation and a tethered spinal cord, respectively, which subsequently were relieved by surgical procedures.

She was developmentally delayed, especially in gross motor skills, which was first noted by 16 months of age. She rolled over at 3 months and sat up at about 8 months. At 16 months of age, she was able to crawl and stand, and she walked starting around 18 months. She was not yet talking but did make some noises and started her first occupational and physical therapy at 16 months of age. At 6 years of age, she is in the first grade and has been

receiving special education services with an IEP under the category of global developmental delay. She receives speech, occupational, and physical therapy through school. Her speech therapist noted that she has severe receptive expressive language impairment. Her full-scale IQ score was 67 with relative strength in her visual spatial skills and relative weakness in verbal comprehension skills. She also was diagnosed with attention deficit/hyperactivity disorder (ADHD) and borderline intellectual functioning.

At her 6-year-old evaluation her weight was 23.1 kg (69th percentile); her height was 113.5 cm (20th percentile), and her head circumference was 48.2 cm (10th percentile). Due to unclear speech, her words were noted to be challenging to understand. She had mild dysmorphic features including epicanthal folds, mildly flat nasal root, malar hypoplasia, and a long philtrum (Figure 1). Her ears were normally set with residual ear tags. There was mild hypoplasia of the helices bilaterally. Limb examination revealed a short fifth right metacarpal and mild clinodactyly of the fifth fingers bilaterally. There was clinodactyly of toes 3, 4, and 5 bilaterally.

The family history is significant on both sides (Figure 2). Her mother and maternal half-uncle have learning disabilities. Her father's history is significant for learning disabilities, affective disorder, seizure disorder, abnormal speech (described as nasal and hypophonic, with normal language), and Tourette syndrome. Paternal grandparents are negative for these features. Her paternal aunt has a history of unspecified neurologic and psychologic issues. The proband's older sister has learning and behavioral difficulties at school and is diagnosed with ADHD, although her learning difficulties are much milder than the proband.

3 | RESULTS

Fragile X molecular testing was performed and was negative. Chromosomal microarray (CMA) analysis was performed on genomic DNA from peripheral blood using the Applied Biosystems CytoScan HD array platform (ThermoFisher Scientific, Carlsbad, CA) and identified a 9.8 Mb deletion at 7q31.2-q31.33 (arr[hg19] 7q31.2-q31.33 (114,888,786-124,720,929)x1), including 75 total genes and 32 OMIM genes (Table S1). According to the most recent ACMG technical standard,[20] this variant is classified as pathogenic (score >0.99). Subsequently, familial CMA studies were performed for the proband's father, mother, older sister, and paternal grandmother and revealed the same deletion was present in only her father. Her paternal grandfather was unavailable for testing. Written informed consent was obtained from the proband and her family

FIGURE 1 Photographs of the proband at 6 years and 5 months. Note mild dysmorphic features including epicanthal folds, mildly flat nasal root, malar hypoplasia, and a long philtrum, hypoplasia of the helices. Limb examination showed a short fifth metacarpal on the right and bilateral mild clinodactyly of the fifth fingers.

for testing and publication of clinical data, as approved by the institutional review board at Indiana University (IRB#1811364611).

4 | DISCUSSION

We describe a girl who has a paternally inherited 9.8 Mb deletion at 7q31.2-q31.33, located 550 kb downstream of the *FOXP2* gene, with features including speech and language impairment, global developmental delay, learning difficulties, relative microcephaly, ADHD, and mild dysmorphic features. The deletion was inherited from her father who has a history of learning disabilities, affective disorder, seizure disorder, abnormal speech, and Tourette syndrome. While most of the reported deletions in this region include the *FOXP2* gene, there are a few reported individuals with speech and language impairment who carry a ~3–5 Mb deletion located near but not including *FOXP2* (Figure 3). A 4.7 Mb deletion at 7q31.2q31.31, overlapping our proband's deletion, has been reported in three members of a family with speech and language issues, learning difficulties, microcephaly, and ADHD.[19] The shared deleted region contains 13 OMIM genes, and both deletions are located 550~600 kb downstream of the *FOXP2* gene. In addition, a 3.2 Mb deletion overlapping our proband's deletion has been identified in a girl with developmental delay and hearing loss.[1] Although clinical information was limited, the girl also has delayed speech and language development. The 3.2 Mb deletion is located 1300 kb downstream of the *FOXP2* gene and contains the same 13 OMIM genes. Overlapping phenotypes of these affected individuals suggest that these deletions likely share a common molecular pathogenesis relating to speech and language development. In addition to these published cases, there is one de novo deletion case in the
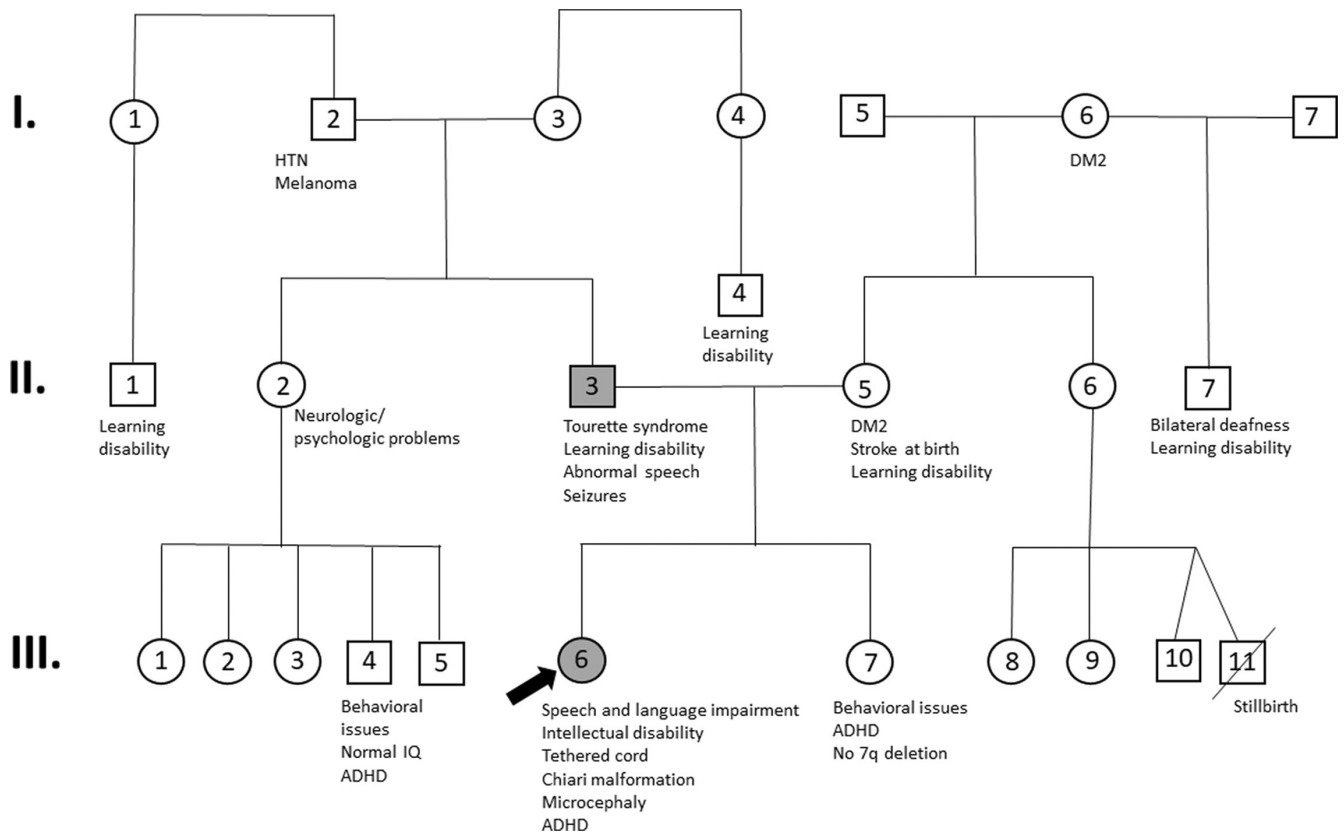
FIGURE 2 Pedigree of 7q31 deletion. The proband (III-6) and her father (II-3) with 7q31 deletion are indicated by solid gray shading. This sibling (III-7), mother (II-5), and paternal grandmother (I-3) tested negative for the deletion. No other family members were available for testing. ADHD, attention deficit hyperactivity disorder; DM2, diabetes mellitus type 2; HTN, hypertension.
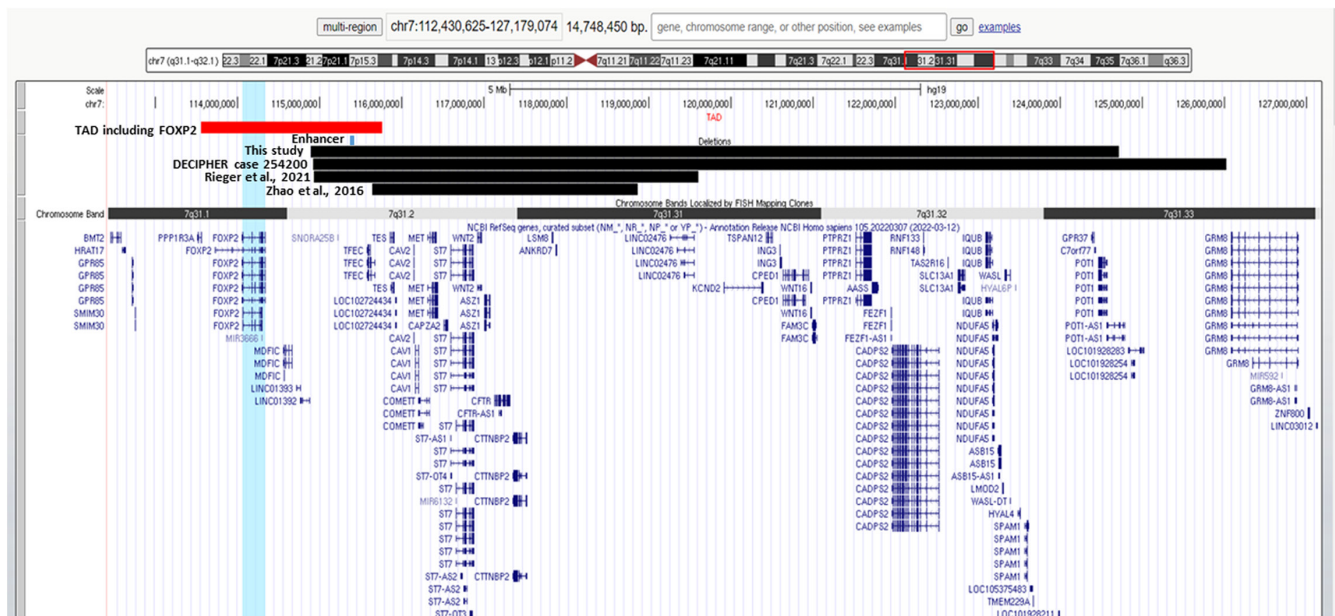

FIGURE 3 Schematic overview of the chromosome 7q31 region from the UCSC Genome Browser[38] with the *FOXP2* gene highlighted in light blue. Black bars represent deletions found in individuals from our study,[1,19] and DECIPHER case 254,200. The blue bar shows an experimentally validated enhancer in the VISTA enhancer database.[35] The red bar shows the topologically associated domain (TAD) that includes *FOXP2* and partially overlaps the deleted regions.

DECIPHER database (patient 254,200) with similar breakpoints to our proband's deletion, although no phenotypic information was provided.

The 13 OMIM genes in the deleted region shared among these previously reported patients and the current patient were reviewed in previous studies and in our study.[1,19] Among them are three disease-causing genes, *CFTR*, *MET*, and *CAV1*. None of these genes have been implicated yet in language development. *CFTR* is associated with autosomal recessive cystic fibrosis (OMIM #219700), and congenital bilateral absence of vas deferens in males (OMIM #277180). *MET* is a proto-oncogene associated with papillary renal cell carcinoma 1 (OMIM #605074), and *CAV1* is associated with primary pulmonary hypertension (OMIM #615343) and lipodystrophies (OMIM #606721 and #612526). The individuals in the current study do not have any clinical signs suggesting these disorders.

Among the remaining 10 OMIM genes, *CAPZA2* and *ST7* are predicted to be intolerant to loss of function (pLI score = 1), and *CAPZA2* has implications in neurological phenotypes. *CAPZA*2 is one of numerous capping proteins that regulates the elongation and depolarization of actin filaments at the fast-growing end. Two heterozygous missense variants in *CAPZA2* were identified in two unrelated individuals presenting with developmental delay, speech delay, intellectual disability, hypotonia, and seizures.[21] Patient-identified variants showed both mild loss of function and dominant negative effects in *Drosophila*. A third patient was recently reported with an in-frame deletion of *CAPZA2*, and a phenotype including global developmental delay and secondary microcephaly.[22] Thus, a pathogenic contribution of *CAPZA2* hemizygosity cannot be completely excluded in our proband's phenotypes, while supporting data for haploinsufficiency of this gene is very limited. *CTTNBP2* is an actin cytoskeleton regulator and is exclusively expressed in the brain with high accumulation at dendritic spines.[23,24] Variants in *CTTNBP2* have been linked to autism spectrum disorders (ASD).[25-28] However, the pLI score in gnomAD (v.2.1.1) is 0[29] and the clinical significance of a heterozygous deletion of this gene remains unclear.

In addition to the genes discussed above, the 9.8 Mb deletion found in our proband contains 19 other OMIM genes. These include three disease-causing genes (*TSPAN12*, *AASS*, and *FEZF1*), associated with autosomal dominant exudative vitreoretinopathy 5 (OMIM #613310), autosomal recessive hyperlysinemia type I (OMIM #238700), and autosomal recessive hypogonadotropic hypogonadism 22 with or without anosmia (OMIM # 616030), respectively. These genes currently have no known implications in speech disorders or cognitive impairment. *ING3*, *PTPRZ1*, and *FEZF1* are predicted to be intolerant to loss of function (pLI≥0.9), though they have no known association with speech disorders. Variants in the calcium-dependent activator protein for secretion 2 (*CADPS2*) gene have been found in individuals with intellectual disability and ASD.[30] However, the pLI score in gnomAD (v.2.1.1) is 0.37 and the clinical significance of hemizygosity for this gene is unknown.

Since chromosome 7 is known to harbor a number of differentially methylated genes, we evaluated whether any of the deleted genes could be associated with an imprinting effect. To date, there are three known imprinted regions distributed along chromosome 7. These are clustered in regions located at 7p11.3-p15.3, 7q21, and 7q32, and none overlap with the deletion observed in our proband.[31] While there are no known imprinted genes in the deleted region, it is notable that one study has suggested *FOXP2* is subject to the epigenetic mechanism of random monoallelic expression (RMAE), where some cells in the body express only the maternal allele and others express only the paternal allele.[15] Thus, it is possible that a mechanism other than haploinsufficiency plays a role in the phenotypic manifestations of *FOXP2*-related disorders.

Given the absence of definitive candidate genes within the deletion for the proband's phenotypes, we propose the *FOXP2* gene is involved in our proband's language-related phenotypes via a positional effect, in agreement with the previously reported case.[19] *FOXP2* may be also responsible for proband's other features such as developmental delay and cognitive impairment that falls within a broad spectrum of *FOXP2*-related disorders.[3] The proband's father has a history of learning issues, seizures, abnormal speech, and Tourette syndrome, which suggests variable expressivity. To date, all reported cases of *FOXP2*-related disorder have been fully penetrant, but there is considerable intrafamilial and interfamilial variability of both speech impairment and cognitive ability.[3]

Alternatively, other genes within the deletion may be causing these phenotypes. Features such as autism spectrum disorder and global developmental delay are more common in individuals with large deletions including *FOXP2* and other neighboring genes compared with those carrying variants affecting only *FOXP2*, suggesting potential clinical significance of neighboring genes (Morgan, Fisher, Scheffer, & Hildebrand, 2016), although we do not currently have any strong candidate genes for these phenotypes. Disruption of non-coding regulatory elements of *FOXP2* has been a proposed mechanism in cases of structural variation such as balanced translocation or inversion with breakpoints near the gene.[16-18] Experimental confirmation of transcriptional effects on the gene has thus far been impossible or inconclusive as *FOXP2* expression level is very low in easily accessible tissues such as peripheral blood and skin fibroblasts.[18,19]

Although it is not fully understood how the gene expression is controlled via cis-regulatory elements outside of the coding region, putative enhancers of *FOXP2* have been identified, some of which show enhancer activities by functional assays.[16,32,33] These reported enhancers are in close proximity to *FOXP2*, and none of them are within the deleted genomic region in our proband. It is known that regulatory elements generally can be present as much as 1 Mb in either direction from the transcription unit.[34] The VISTA enhancer database showed that there is one experimentally validated enhancer within the deleted region that is located ~1 Mb downstream of *FOXP2* (Figure 3),[35] and it may be possible that this plays a role in regulating *FOXP2* transcription. Alternatively, this deletion may alter 3D chromatin structure around *FOXP2*, which may perturb interactions of critical chromatin sites for the gene regulation. *FOXP2* and a part of the deletion in our proband are within the same topologically associated domain (TAD) where preferential internal interactions of chromatin occur[36] (Figure 3). It has been shown that large deletions can influence local chromatin structure while effects are variable by locus[37]; therefore, further investigation on the effects of this deletion on chromatin structure is needed.

In conclusion, we report a paternally inherited 9.8 Mb deletion at 7q31.2-q31.33 in a girl with speech and language impairment, developmental delay, learning difficulties, relative microcephaly, ADHD, and mild dysmorphic features. Her father who carries the same deletion has overlapping but distinct features, suggesting variable expressivity. The molecular mechanism causing these clinical features remains to be fully elucidated. Functional studies and additional cases with similar deletions will help us better understand the clinical significance of this genomic region.

AUTHOR CONTRIBUTIONS

Aiko Iwata-Otsubo performed molecular analysis, original draft preparation, reviewed, and edited the manuscript. Victoria H. Klee counseled the proband and family and participated in the revision of the manuscript. Aaliya A. Ahmad counseled the proband and family and participated in the revision of the manuscript. Laurence E. Walsh examined the proband and participated in the revision of the manuscript. Amy M. Breman performed molecular analysis, original draft preparation, reviewed, and edited the manuscript.

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CONFLICT OF INTEREST

None.

CONSENT

Written informed consent was obtained from the proband to publish this report in accordance with the journal's proband consent policy.

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