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CASE REPORT

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Subtelomeric microdeletion in chromosome 20p13 associated with short stature

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Key Clinical Message

Among the total 10 reported cases with 20p13 microdeletion, including our patient, it is notable that 50% of patients presented a height below the 3rd percentile. We suggest that short stature is among the most common manifestations in patients with 20p13 subtelomeric microdeletion.

Abstract

Chromosome 20p13 microdeletion occurs rarely, with only 10 reported cases. We report a 16-year-old male with a 1.59 Mb terminal deletion in chromosome 20p13, who presented with proportionate short stature, mild language delay, mild learning disability, and delayed puberty. The clinical phenotype associated with this deletion can exhibit clinical variability. Our patient deviates from the typical developmental and intellectual phenotype seen in the 20p13 deletion, instead displaying mild speech delay, short stature, and delayed puberty. The *CSNK2A1* deletion, leading to haploinsufficiency, might be the potential mechanism. And the prominence of his proportionate short stature provides a unique perspective to review the existing literature.

KEYWORDS

CSNK2A1, delayed puberty, ear pits, microdeletion 20p13, short stature, speech delay

1 | INTRODUCTION

Distal deletion of chromosome 20p frequently encompasses *JAG1*, which is responsible for approximately 7% of Alagille syndrome cases.[1] Microdeletion of 20p13 not encompassing *JAG1* is less common, first described in 2010.[2] A total of 10 patients with 20p13 deletion not involving *JAG1* have been reported.[2–7] The sizes of these microdeletions vary from 799 kb to 2.08 Mb, leading to diverse clinical presentations. However, patients with such deletions commonly share some clinical features such as motor and language delays, intellectual disability, EEG abnormalities, seizure, dysmorphic features, abnormal digits, and a large fontanelle.[4]

We presented a patient with a 1.59 Mb subtelomeric microdeletion in 20p13 who presented with mild neurological features and proportionate short stature. Additionally, we reviewed the growth parameters of 9 previously reported patients with overlapping subtelomeric microdeletion in 20p13.

2 | CASE HISTORY/EXAMINATION

A 16-year-old African American male was referred to the Genetics clinic for evaluation of short stature. The patient was born at full term to a 24-year-old G5P5 mother via vaginal delivery. The pregnancy and delivery were uncomplicated. Birth weight and length are unknown. He has been small since birth. Motor development was reported to be normal. He has a mild language delay and has been receiving speech therapy through school once a week, and he is in a regular 9th-grade class.

On examination at 16 years of age, age-based growth parameters showed height at <1st percentile (142.5 cm), weight at <1st percentile (31.8 kg), and head circumference at the 8th percentile (53 cm). He had low-set and posteriorly rotated ears, a right preauricular ear pit, hypertelorism, low posterior hairline, right eye exotropia, micrognathia, and pectus carinatum. Findings on cardiovascular examination and echocardiogram were unremarkable. His extremities, fingers, and toes were normal in appearance. He had not developed secondary sexual characteristics. Bone age study was reported to be normal.

3 | METHODS

Array Comparative Genomic Hybridization (aCGH) was performed using the Agilent 4×180K CGH+SNP microarray (Agilent Technologies, Santa Clara, CA). RASopathies and Noonan Spectrum Disorders Panel used a hybridization-based protocol and sequenced using Illumina technology, which includes 28 genes. Whole exome sequencing (WES) was performed on enriched DNA with complete coding regions and splice site junctions for most genes of the human genome, and paired-end reads were performed on an Illumina platform. NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19 were used as reference sequences database.

4 | CONCLUSION AND RESULTS

An aCGH demonstrated an approximately 1.59 Mb deletion in chromosome 20p13 subtelomeric (genomic coordinates 102,422 - 1,691,755 [GRCh37]). This deletion encompasses 37 protein-coding genes, 22 of which are OMIM genes. A second deletion of approximately 325 kb in chromosome 8q23.1 (genomic coordinates 107,715,532 - 08,040,768 [GRCh37]) was also detected. This deletion encompasses 2 protein-coding genes, *OXR1* and *ABRA*. RASopathies and Noonan Spectrum Disorders Panel showed a negative result. Whole Genome Sequencing (WES) detected a heterozygous pathogenic multi-gene deletion within cytogenetic band 20p13, which spans a region of 1119 kb in size. Genomic coordinates are chr20:68350_1187747 [GRCh37]. This finding is consistent with reported clinical features and the results from aCGH. His father was negative for this deletion. The mother was not available for testing.

5 | DISCUSSION

Subtelomeric microdeletion of 20p13 excluding *JAG1* is rare. The specific effects and symptoms of this deletion can vary depending on the size and location of the deletion, as well as individual factors. Fang et al. outlined the typical feature associated with 20p13 deletion, highlighting motor delay as the most common manifestation observed in 90% of cases. Subsequently, language delay was reported in 60% of cases, followed by abnormal digits, mental retardation, large fontanelle, EEG abnormalities, and seizure.[4] To date, there is no established haploinsufficient gene in this deleted region. However, missense mutations in *CSNK2A1* (casein kinase 2 alpha 1) in the deleted region have been recently identified as the cause of an autosomal dominant Okur-Chung neurodevelopmental syndrome (OCNDS; OMIN #617062). *CSNK2A1* encodes a kinase protein casein kinase II (CK2α).[8] CK2α is a highly conserved serine–threonine kinase involved in various cellular processes, including cell cycle control, apoptosis, embryonic development, and circadian rhythms.[9] $CK2\alpha^{-/-}$ mice die in the embryonic stage on day 11 (E11), with embryonic defects becoming evident at E9.5. A striking 95% of $CK2\alpha^{-/-}$ mice showed open neural tubes at the midbrain in contrast to 18% of wild-type embryos. Abnormal heart tube, hypoplastic limb buds, and pharyngeal aches were also presented in the $CK2\alpha^{-/-}$ mice.[9] Heterozygous CK2α knock-out mice appear phenotypically normal and have a normal life span. However, no research is available regarding the intellectual and behavioral function of these heterozygous CK2α knock-out mice. Dominguez et al. also reported that cell lines derived from 15 different *CSNK2A1* variants exhibited varying degrees of decreased kinase activity compared to wild-type cell lines; three of the variants (Arg47Gln, Arg312Gln, and Arg312Trp) also showed a lower level of kinase protein expression.[10] These findings suggest that the causative *CSNK2A1* missense mutation in OCNDS is a loss-of-function alteration. The clinical presentations of OCNDS, including delayed psychomotor development, intellectual disability with poor speech, and behavioral abnormalities, are similar to those of 20p13 microdeletion patients, suggesting the potential feature of haploinsufficiency of the *CSNK2A1*.

Another research involving six cases of 20p13 microdeletion suggested that two genes expressed in central nervous system, *SOX12* and *NRSN2*, might be the candidate genes contributing to these patients' clinical features of developmental delay, abnormal EGG, and seizure.[3] *SOX12*, a member of the SOX gene family of transcription factors, along with Sox4 and Sox11, are collectively referred to as SoxC proteins.[11] The human *SOX12* (formally referred as *SOX22*) was most abundantly expressed in the central nervous system during embryonic development.[12] However, SOX12$^{-/-}$ mice showed normal embryonic development without gross phenotypic abnormalities and normal postnatal growth.[11] The second candidate gene, *NRSN2*, encodes a protein known as Neurensin-2, which is a small neuronal membrane protein.[13] This gene is broadly expressed across 24 human tissues, with the highest expression observed in brain tissue [NIH, Gene ID: 80023].[13] However, there is no direct evidence supporting the mutation or deletion of either *SOX12* or *NRSN2* leading to a human neurologic disorder based on the ClinVar database. Further studies on the genes and protein function are necessary to validate the genotype–phenotype relationship.

Our case has 1.59 Mb deletion at 20p13, encompassing 37 protein-coding genes, 22 of which are OMIM genes (Figure 1), including *CSNK2A1*, *SOX12*, and *NRSN2*. However, our patient notably lacks most of the common clinical features associated with developmental defects and intellectual disability. The primary manifestation is mild language delay. Following regular speech therapy once a week, he is performing well in a regular school and does not exhibit signs of intellectual disability. His facial features, including hypertelorism, low-set ears, and micrognathia, are consistent with previously reported cases.[4,7] However, ear pits, low posterior hairline, and pectus carinatum have not been reported in individuals with chromosome 20p13 deletion.

On the other hand, our patient exhibited pronounced proportionate short stature (height and weight were <1st percentile). Upon reviewing the

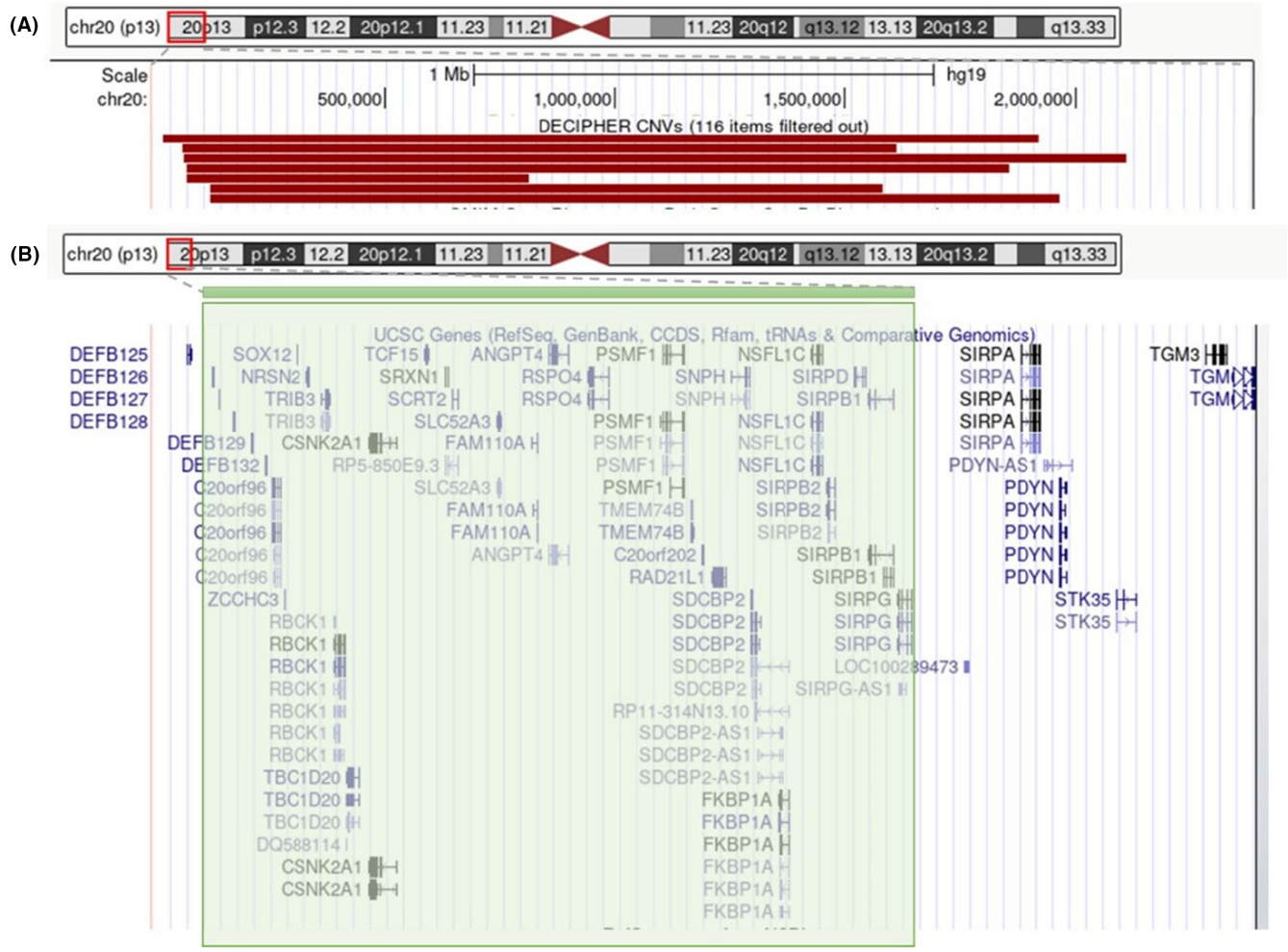

FIGURE 1 Schematic view of chromosome 20p13 microdeletion. (A) Similar microdeletion cases which have been reported on DECIPHER database as pathogenic variants. (B) Mapping the microdeletion region of our case and showing all the deleted genes in a green shadow box.

literature, it became evident that short stature should also be considered as a common manifestation of 20p13 microdeletion patients without involvement of *JAG1*. Among the total of 10 such cases, including our patient, it is notable that 50% of patients presented a height below the 3rd percentile, and 30% of the patients exhibited a height between the 3rd and 10th percentile. Furthermore, 30% and 20% of the patients exhibited body weight below the 3rd and between the 3rd and 10th percentile, respectively (Table 1). The majority of the patients had normal head circumference. We excluded the case reported by Kwon et al., because the specific patient contained an additional 6.6 Mb pathogenic duplication in chromosome 12p13, which could complicate the study of genotype–phenotype correlation. The specific genetic cause for the observed short stature in these patients is still unclear. Further studies of gene and protein function are crucial to comprehending the mechanisms and pathogenesis underlying this phenotype.

Our patient exhibited a second variant of a 325 kb deletion in 8q23.1. There were two genes included in this deleted region, *OXR1* and *ABRA*. The *OXR1* (OMIM:605609) encodes a protein with a predicted oxidoreductase activity. Five cases with compound heterozygous or homozygous variants of the *OXR1* have been reported, which manifested as cerebellar hypoplasia/atrophy, epilepsy, and global developmental delay.[14] However, there have been no reported clinical phenotypes associated with the monoallelic variant of *OXR1*. Therefore, the haploinsufficiency of this gene is a variant of uncertain significance. *ABRA* (OMIM:609747) encodes an actin-binding Rho-activating protein. Several single nuclear variants have been documented in ClinVar, with classifications as uncertain significance or likely benign. No specific phenotype or disease has been identified in connection with the reported variants in *ABRA*. Therefore, the microdeletion in 8q23.1 may not be a contributing factor to our patient's specific phenotype.

In summary, our patient with a 1.59 Mb subtelomeric microdeletion exhibits much milder developmental and intellectual defects in comparison to previously reported cases, though the size of the deletion shares the same range as other 20p13 subtelomeric microdeletion cases. A review of the literature and ClinVar database suggests that *CSNK2A1* has the potential to be the haploinsuffient gene in 20p13 microdeletion patients. Notably, we suggest that short stature is among the most common manifestations in patients with 20p13 subtelomeric microdeletion. Our findings contribute to a better understanding of this genomic region and a further correlation of the phenotypes with 20p13 deletions.

TABLE 1 Growth parameters of the reported 20p13 microdeletion patients.

	Age	Gender	Weight (percentile)	Height (percentile)
McGill (2010)-1	11 months	Female	8.26 kg (25th)	**66 cm (<3rd)**
McGill (2010)-2	15 years 4 months	Female	*40.6 kg (3rd)	**145.6 cm (<3rd)**
Moutton (2012)	19 years	Female	51 kg (21st)	*154 cm (8th)
Jezela-Stanek (2012)	11 years	Male	**23 kg (<3rd)**	**130 cm (<3rd)**
An (2013)-1	14 years 9 months	Male	63 kg (75th)	165.9 cm (60th)
An (2013)-2	9 years 8 months	Male	36.2 kg (79th)	129.4 cm (11th)
An (2013)-3	2 years 4 months	Female	*11.8 kg (10th)	*86.5 cm (10th)
An (2013)-4	8 years 8 months	Male	22.3 kg (10th–25th)	*121.2 cm (3rd–10th)
Fang (2019)	7 months	Female	**5.8 kg (<3rd)**	**62 cm (<3rd)**
Our case	15 years 2 months	Male	**31.8 kg (<1st)**	**142.5 cm (<1st)**

Note: The symbol of *highlighted the parameter between the 3rd and 10th percentile. Bold highlighted the parameter below the 3rd pencentile.

AUTHOR CONTRIBUTIONS

J. Liu: Writing – original draft; writing – review and editing. **Y. Li:** Writing – review and editing. **H. C. Andersson:** Writing – review and editing. **J. Upadia:** Writing – original draft; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association, updated in 2013.

CONSENT

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

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