Clinical Case Report

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A boy with 13.34-Mb interstitial deletion of chromosome 4p15

A new case report and review of the literature

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Abstract

Rationale: To date, >40 cases have been described with interstitial deletions involving the 4p15 region.

Patient concerns and diagnosis: We report a case of a 3-year-old boy with an interstitial de novo deletion of approximately 13.34 Mb in 4p15.1–15.31 having mild developmental delay and multiple minor congenital abnormalities.

Lessons: This case presents a clinical manifestation that is similar but not identical to other reported cases. In this report, we have provided a detailed description of a 3-year-old patient with an interstitial 4p deletion and mildly affected phenotype. We discuss the possible involvement of *SLIT2*, *KCNIP4*, and *LGI2* in cortical development and *RBPJ* in skeletal abnormalities.

Abbreviations: CGH = comparative genome hybridization, CNS= central nervous system, KCNIP4 = potassium channel-interacting protein 4 isoform, LGI2 = leucine-rich glioma inactivated protein 2, OMIM = Online Mendelian Inheritance in Man, PCDH7 = procadherin 7 isoform c precursor, RBPJ = recombination signal-binding protein for kappa J region, SLIT2 = slit homolog 2, SNP = single-nucleotide polymorphism, WHS = Wolf-Hirschhorn syndrome.

Keywords: 4p deletion, developmental delay, minor congenital abnormalities

1. Introduction

Previously interstitial deletions of chromosome 4p have only been rarely described. Deletions encompassing the 4p15 region result in a distinct clinical syndrome, different from Wolf-Hirschhorn syndrome (WHS, Online Mendelian Inheritance in Man 194190). The main clinical features of previously reported cases are mild to moderate mental retardation and multiple minor dysmorphic features such as a long face, up-slanted palpebral fissure with epicanthal folds, large lax lips, pectus excavatum, and tall and thin body habitus [1–8]. To date <40 cases with 4p15 deletions have been reported and in approximately 4 cases the extent of the deletion was ascertained through array comparative genomic hybridization. In this study, we report a 13-Mb interstitial deletion of 4p15.1–15.31 in a patient with mild psychomotor retardation and minor dysmorphic features.

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2. Clinical report

The patient is a 3-year-old boy. He is the first child of a healthy, young nonconsanguineous white couple: the respective family histories of parents were negative for developmental, congenital, genetic or neurologic disorders. The mother was diagnosed with thrombophilia in the second trimester of pregnancy and she had received anticoagulant treatment. The delivery occurred at 40 weeks of gestation and was uneventful. His birth weight was 3600 g and birth length was 51 cm; his Appearance, Pulse, Grimace, Activity, Respiration scores were 9 and 10 at 5 and 10 minutes. His development was slightly retarded. He could hold his head at the age of 6 months and sit at the age of 9 months. He started to walk at the age of 16 months and used single words at the age of 30 months. He was clinically evaluated at the age of 33 months because of unusual physical findings and developmental delay. During his physical examination, a long face with a high forehead, deep-set eyes, puffy eyelids, broad and flat nasal bridge, lateral flaring of the nostrils, long philtrum, and a thick and proeminent lower lip were recorded (Fig. 1). His teeth were normal and his palate was high arched and intact. His skin showed one café-au-lait spot (2,5/3ï¿1/2cm in diameter) on the right thigh. His ears consisted of proeminent and thick lobes, and they were very close to his heade. His height was 97 cm (75th centile), his weight was 16 kg (90th centile), and his head circumference was 48 cm (10th centile). He had pectus excavatum, broad hands and feet, and clinodactyly of the toes. The proband also presented with a left undescended testis and required a surgical intervention for phimosis. His medical history included frequent upper respiratory infections and bronchiolities.

3. Methods

The patient's parents provided an informed consent to publish all clinical information. The report was approved by the local commission for the approval of clinical and reasearch developmental studies.

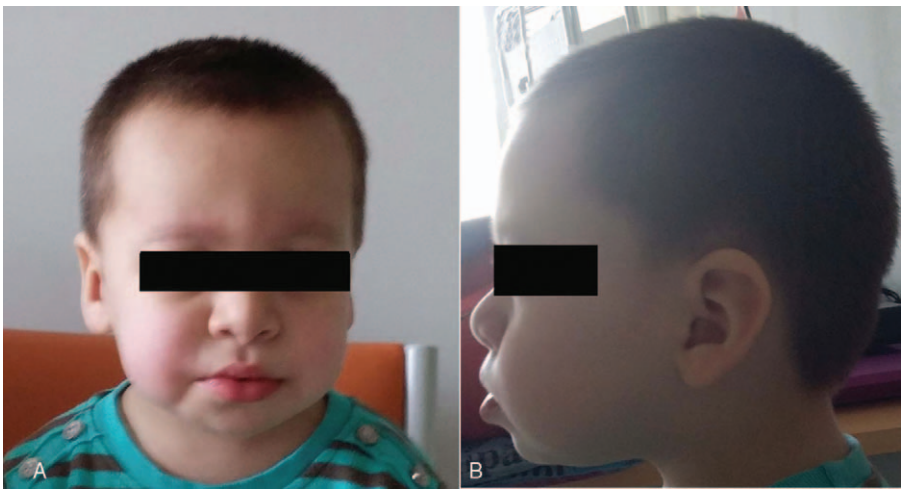

Figure 1. Proband at 3-year-old face (A) and profile (B). Note the long face, high forehead, puffy eyelids, broad and flate nasal bridge, long filtrum, thick and proeminent lower lip.

3.1. Cytogenetic analysis

Cytogenetic analysis was conducted on G-banded metaphases of cultured peripheral lymphocytes in accordance with standard protocols. Metaphases were analyzed at the 400 to 500-band resolution level. The karyotype was described in accordance with the guidelines of the 2016 International System for Human Cytogenetic Nomenclature.

3.2. Array-comparative genome hybridization

For the precise delineation of the deleted region array-comparative genome hybridization (CGH) was conducted using an Agilent Sure Print G3 Human Genome CGH + SNP, 4 × 180K, Microarray Kit in accordance with the manufacturer's protocols. Images were scanned using Sure Scan from Agilent and analyzed using the Feature Extraction and CytoGenomics software programs.

4. Results

The karyotype was 46,XY,del(4)(p15.3p15.1),9qh+ (Fig. 2A). The parental karyotypes were normal. Array-CGH analysis revealed a deletion on chromosome 4p15.1–15.31, which confirmed the karyotype (Fig. 2B). The deleted region was estimated to be 13.34 Mb (chromosome position: 19,108,480–32,448,650) and contained 29 genes (Table 1).

5. Discussion

Interstitial deletion of the short arm of chromosome 4 can lead to several clinical syndromes. Deletions which encompass the 4p16.3 region lead to Wolf-Hirschhorn syndrome, which results in a clinically significant phenotype [8]. Patients with deletion in the 4p15 region present a clinical phenotype different from that of mild and classic Wolf-Hirschhorn syndrome: proximal 4p deletion, characterized by normal growth with psychomotor retardation, multiple minor congenital abnormalities, and a characteristic face. Our patient presented like other reported cases normal growth with slight psychomotor retardation, pectus excavatum, left undescended testis, clinodactyly of the toes, and a somewhat characteristic facial dysmorphism including a long face, deep set eyes, puffy eyelids, flat and broad nasal bridge, long philtrum, and full lips[1–8]. Unlike other reported cases, our

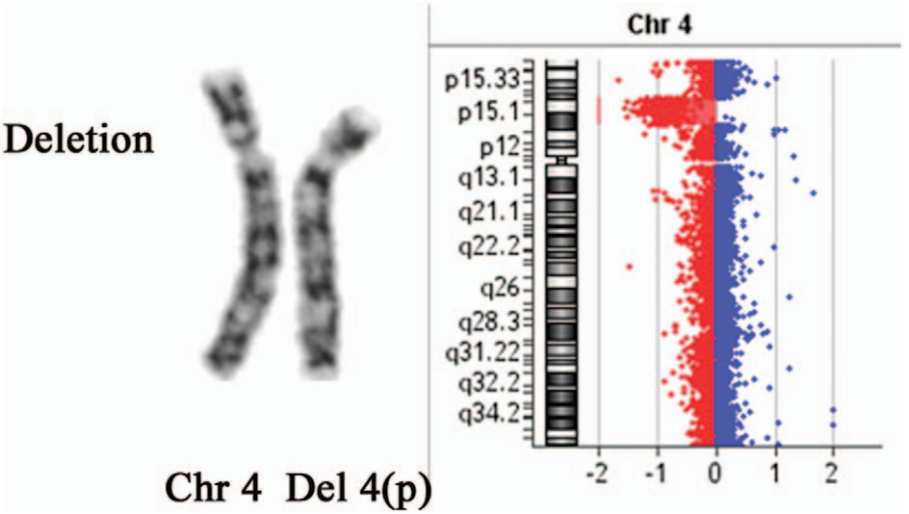

Figure 2. Cytogenetics analysis (A) and array comparative genome hybridization (B) results of the interstitial deletion of 4p15.1–15.31.

Table 1

Genes deleted in the 4p15.1–15.31 region in the presented case.

Gene	OMIM	Protein/transcript name	Function/dysfunction of gene product
SLIT 2	603746	Slit homolog 2	Molecular guidance cue in cellular migration, interact with roundabout homolog receptors
KCNIP4	608182	Potassium channel-interacting protein 4 isoform	Regulatory subunit of Kv4/D (Shal)-type voltage-gated rapidly inactivating A-type potassium chanel
GPR125	612303	G protein-coupled receptor 125	Orphan receptor that may play a role in planar cell polarity pathway
GBA3	606619	Glycosidase beta acid 3	Glycoidase probably involved in intestinal absorption and metabolism of flavnoid glycosides and beta-glycosylceramidase activity
PPARGC1A	604517	Peroxisome proliferative activated receptor gamma	Transcriptional coactivator for steroid receptors and nuclear receptors
DHX15	603403	DEAH box polypeptide 15	Nuclear ATP-dependent helicase
SOD3	185490	Superoxide dismutase 3	Free radical detoxification
LGI2	608301	Leucine-rich glioma inactivated protein 2	May be involved in axonal path finding
SEPSECS	613009	O-phosphoserin tRNA-selenocystein tRNA syntase	Pontocerebellar hypoplasia type 2D (AR)
PI4K2B	612101	Phosphatidylinositol 4-kinase type 2 beta	Phosphatidylinositol 4-kinase type 2 beta
ZCCHC4	611792	Zinc finger CCHC domain-containing protein 4	May be a methyltransferase
ANAPC4	606947	Anaphase-promoting complex subunit 4	Component of anaphase-promoting complex/cyclosome, a cell cycle regulated E3 ubiquitin ligase and the G1 phase of the cell cycle
SLC34A2	604217	Sollute carrier family 34 (sodium, phosphate cotransporter) member 2	Testicular microlithiasis. Pulmonary alveolar microlithiasis (AR)
RBPJ	147183	Recombination signal-binding protein for kappa J region	Adam-Oliver syndrome 3 (AD)
CCKAR	118444	Colecystokinin A receptor	Receptor for cholecystokinin with role in colecystokinin induced regulation of satiety
PCDH7	602988	Procadherin 7 isoform c precursor	Mediation of calcium dependent cell-cell adhesion expressed predominantly in SNC
STIM2	610841	Stromal interaction molecule 2	Regulation of basal cytosolic and endoplasmic reticulum Ca^{2+} concentrations
LOC100505893	—	Hytpothetical protein LOC100505893	Function unknown
MIR 218–1	—	microRNA 218–1	Non-coding RNAs—miRNA
PACRGL	—	PACRG- like protein	Function unknown
NCRNA00099	—	KCNIP4 intronic transcript 1	lincRNA
LOC100505912	—	Hytpothetical protein LOC100505912	Function unknown
MIR573	—	microRNA573	Non-coding RNAs—miRNA
CCDC149	—	Coiled-coil domain containing protein 149	Function unknown
LOC285540	—	Hytpothetical protein LOC100505912	Function unknown
SEL1L3	—	Protein sel-1 homolog 3	Integral component of membrane
C4ORF52	—	Small integral membrane protein 20	Integral component of membrane
TBC1D19	—	TBC1 domain family member 19	GTP-ase activating protein for Rab family protein
MIR4275	—	microRNA573	Noncoding RNAs—miRNA

OMIM = Online Mendelian Inheritance in Man.

patient did not have a thin body habitus, up-slanted palpebral fissures, or midface hypoplasia. Chitayat et al[3] proposed that for proximal 4p syndrome, the minimal deleted segment was represented by (4)(p15.2p15.33); in our patient, this region was not completely deleted.

Moller et al[7] reported a case with the same deleted region at 4p15.1–15.31 in a 38-year old woman with mild mental retardation, divergent strabismus, enlarged lower lip, tooth irregularities, pectus exaecvatum, bilateral genu valgum, hypermobile joints, and late-onset epilepsy with generalized tonic-clonic seizures. In addition, she presented with polymicrogyria adjacent to an arachnoid cyst of the left temporal lobe[7] and the deletion was approximately 15Mb and spanned other chromosome positions. The genes such as *SLIT2* (Slit homolog 2), *KCNIP4* (potassium channel-interacting protein 4 isoform), and *LGI2* (leucine-rich glioma inactivated protein 2) reported by Moller et al of special interest with regard to brain development and epilepsy are also deleted in our case. Another gene, *PCDH7* (procadherin 7 isoform c precursor), which is also deleted in our case, mediates calcium-dependent cell–cell adhesion and is expressed predominantly in CNS, specifically in thalamocortical circuits and the hippocampus, and was reported to be a candidate gene for a common form of epilepsy in a recent study[9]. At present, our patient has not developed epilepsy and does not have congenital brain malformation visible on a brain computerized tomography scan. The presence of developmental delay and intellectual disability in both cases suggests the importance of these genes in cortical development.

Heterozygous missense mutations of *RBPJ* (recombination signal-binding protein for kappa J region) are implicated in Adam Oliver syndrome type 3, a disorder characterized by vertex scalp defect (aplasia cutis congenita) in combination with terminal transverse limb defects[10]. Our patient does not present vertex scalp defect, but has clinodactyily of the toes. *RBPJ*, the principal DNA-binding partner of the Notch intracellular domain, is an evolutionarily conserved protein that coordinates the transcriptional activation of Notch-target genes through the assembly of protein complexes containing coactivators. RBPJ-mediated NOTCH signaling is also important for mesenchyimal cell proliferation, skeletal formation [11] epidermis, and hair follicle development [12] and vascular structure formation.[13] Furthermore, RBPJ- deficient mice have defective cranial bone formation [14]. Therefore, the deletion of the *RBPJ* contributes to or is responsible for other skeletal abnormalities observed in cases of

interstitial 4p deletions such as pectum excavatum and/or long face with high forehead.

In this report, we have provided a description of a 3-year-old patient with interstitial 4p deletion and mildly affected phenotype at this current age. He presented with pre- and postnatal normal growth, mild psychomotor retardation, and multiple minor congenital abnormalities. We therefore emphasize the involvement of *SLIT2, KCNIP4* and *LGI2* in cortical development and that of the *RBPJ* in skeletal abnormalities.

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