A boy with 13.34-Mb interstitial deletion of chromosome 4p15
A new case report and review of the literature

Anca Florentina Mitroi, MD, PhD, Marianna Aschie, Prof, MD, PhD, Adriana Apostol, MD, PhD, Costel Brinzan, PhD, Georgeta Cozaru, MD, PhD, Adrian Nelutu Mitroi, MD, PhD

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 habitus1–8. 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.

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 3600g 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 prominent 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 (2.5/3.2cm in diameter) on the right thigh. His ears consisted of prominent and thick lobes, and they were very close to his head. 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 bronchiolitis.

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 research developmental studies.
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\(^1\text{–}^8\). Unlike other reported cases, our
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 woman with mild mental retardation, divergent strabismus, enlarged lower lip, tooth irregularities, pectus excavatum, 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 chromosomes. The genes such as LOC100505893 region was not completely deleted.

Table 1

| 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              |
| KCNJ4           | 608182 | Potassium channel-interacting protein 4 isomor                                           | Regulatory subunit of Kv4D (Shaker) type voltage-gated rapidly inactivating A-type potassium channel |
| GPR125          | 612303 | G protein-coupled receptor 125                                                          | Orphan receptor that may play a role in planar cell polarity pathway                                 |
| GAB3            | 606619 | Glycine O-acetyltransferase beta 3                                                       | Glycine O-acetyltransferase beta 3                                                                  |
| 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                                                                      |
| SOCO3           | 185490 | Superoxide dismutase 3                                                                  | Free radical detoxification                                                                        |
| LG2             | 608301 | Leucine-rich glioma inactivated protein 2                                                 | May be involved in axonal path finding                                                               |
| SEPS1           | 613009 | 0-phosphatidyl-ethanolamine-selenocystein RNA tansante                                   | Postocerebellar hypoplasia type 2 (AR)                                                              |
| FAH             | 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/cytokines, a cell cycle                                     |
| SLC3A42         | 604217 | Solute carrier family 34 (sodium, phosphate cotransporter) member 2                     | Testicular microtubilis. Pulmonary alveolar microtubilis (AR)                                        |
| RBPJ            | 147813 | Recombination signal-binding protein for kapa 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    |       | Hypothetical protein LOC100505893                                                        | Function unknown                                                                                   |
| MIR 218–1       |       | microRNA 218–1                                                                           | Non-coding RNAs—miRNA                                                                             |
| PAG5DL          |       | PAG5δ-like protein                                                                       | Function unknown                                                                                   |
| NONNA00009      |       | KCNJ4 intronic transcript 1                                                              | IncRNA                                                                                              |
| LOC100505912    |       | Hypothetical protein LOC100505912                                                         | Function unknown                                                                                   |
| MIR573          |       | microRNA573                                                                             | Non-coding RNAs—miRNA                                                                             |
| CDDC149         |       | Coiled-coil domain containing protein 14                                                 | Function unknown                                                                                   |
| LOC285540       |       | Hypothetical protein LOC285540                                                           | Function unknown                                                                                   |
| SEL13           |       | Protein sel-1 homolog 3                                                                  | Integral component of membrane                                                                     |
| C4orf52         |       | Small integral membrane protein 20                                                       | Integral component of membrane                                                                     |
| TBCD19          |       | TBC1 domain family member 19                                                            | GTP-ase activating protein for Rab family protein                                                   |
| MIR4275         |       | microRNA573                                                                             | Noncoding RNAs—miRNA                                                                               |

OMIM = Online Mendelian Inheritance in Man.

Copyright © 2017 MG Publishing Group

Heterozygous missense mutations of RBPJ (recombination signal-binding protein for kapa 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 clinodactyly 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 mesenchymal 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.

References

[1] Ishikawa T, Sumi S, Fujimoto S, et al. Interstitial deletion of the short arm of chromosome 4 in a boy with mild psychomotor retardation and dysmorphism. Clin Genet 1990;38:314–7.
[2] Errabooks LL, Rao KW, Korf B. Interstitial deletion of distal chromosome 4p in a patient without classical Wolf-Hirschhorn syndrome. Am J Med Genet 1993;45:97–100.
[3] Chitayat D, Ruvalcaba RH, Babul R, et al. Syndrome of proximal interstitial deletion 4p15: report of three cases and review of the literature. Am J Med Genet 1995;55:147–54.
[4] Fryn JP. Syndrome of proximal interstitial deletion 4p15. Am J Med Genet 1995;58:295–6.
[5] Tonk VS, Jalal SM, Gonzalez , et al. Familial interstitial deletion of chromosome 4 (p15.2p16.1). Am J Genet 2003;46:453–8.
[6] Piovani G, Borsani G, Bertini V, et al. Unexpected identification of two interstitial deletion in a patient with a pericentric inversion of a chromosome 4 and an abnormal phenotype. Eur J Med Genet 2006;49:49215–23.
[7] Møller RS, Hansen OP, Jackson GD, et al. Interstitial deletion of chromosome 4p, associated with mild mental retardation, epilepsy and polymicrogyria of the left temporal lobe. Clin Genet 2007;72:595–8.
[8] Gawalik-Kuklinska K, Wierzbka J, Wozniak A, et al. Periventricular heterotopia in a boy with interstitial deletion of chromosome 4p. Eur J Med Genet 2008;51:165–71.
[9] International League Against Epilepsy Consortium and Complex Epilepsy Genetic determinants of common epilepsies: a meta-analysis of genome wide association studies. Lancet Neurol 2014;13:893–903.
[10] Hassed SJ, Wiley GB, Wang S, et al. RBPJ mutations identified in two families affected by Adams-Oliver syndrome. Am J Hum Genet 2012;91:391–5.
[11] Dong Y, Jesse AM, Kohn A, et al. RBP-Jk-dependent Notch signaling regulates mesenchymal progenitor cell proliferation and differentiation during skeletal development. Development 2010;137:1461–71.
[12] Vaucclair S, Nicolas M, Barrandon Y, et al. Notch 1 is essential for postnatal hair development and homeostasis. Dev Biol 2005;284:184–93.
[13] Dou GR, Wang YC, Hu XB, et al. RBP-Jk, the transcription factor downstream of Notch receptors, is essential for the maintenance of vascular homeostasis in adult mice. FASEB 2008;22:1606–17.
[14] Mead TJ, Yutzey KE. Notch signaling and the developing skeleton. Adv Exp Med Biol 2012;727:114–30.