

Case Report

# Pure partial monosomy 3p (3p25.3 → pter): Prenatal diagnosis and array comparative genomic hybridization characterization

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## Abstract

**Objective:** The purpose of this case report is to present prenatal diagnosis and molecular cytogenetic characterization of pure partial monosomy 3p (3p25.3 → pter) by array comparative genomic hybridization (aCGH) and quantitative fluorescent polymerase chain reaction (QF-PCR) on uncultured amniocytes.

**Case Report:** A 35-year-old, gravida 2, para 0, woman underwent amniocentesis at 19 weeks of gestation because of advanced maternal age. Her husband was 37 years of age. She had experienced one intrauterine fetal death. Amniocentesis during this pregnancy revealed a distal deletion of chromosome 3p. The parental karyotypes were normal. Prenatal ultrasonography findings were unremarkable. At 22 weeks of gestation, she underwent repeated amniocentesis, and aCGH investigation using CytoChip Oligo Array on uncultured amniocytes revealed a 9.29-Mb deletion of 3p26.3p25.3 [arr 3p26.3p25.3 (64,096–9,357,258 bp) ×1] encompassing the genes of *CHLI*, *CNTN4*, *CRBN*, *LRRN1*, *ITPR1*, and *SRGAP3*, but not involving the markers D3S1263 and D3S3594. Polymorphic DNA marker analysis on uncultured amniocytes showed a paternal origin of the deletion. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XX,del(3)(p25.3). At 24 weeks of gestation, prenatal ultrasonography findings of the brain, heart, and other internal organs were unremarkable. The pregnancy was subsequently terminated, and an 886-g female fetus was delivered with brachycephaly, hypertelorism, a short and thick nose, micrognathia and low-set ears.

**Conclusion:** In this case, aCGH has characterized a 3p deleted region with haploinsufficiency of the neurodevelopmental genes associated with cognitive deficit and mental retardation but without involvement of the congenital heart disease susceptibility locus, and QF-PCR has determined a paternal origin of the deletion. aCGH and QF-PCR help to delineate the genomic imbalance in prenatally detected *de novo* chromosome aberration, and the information acquired is useful for genetic counseling.

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**Keywords:** 3p deletion syndrome; *CHLI*; *CNTN4*; *CRBN*; *ITPR1*; *LRRN1*; mental retardation; monosomy 3p; prenatal diagnosis; *SRGAP3*

## Introduction

The 3p deletion syndrome (OMIM 613792) is a contiguous gene syndrome associated with partial monosomy 3p (3p25 → pter) and the characteristic phenotypic features of

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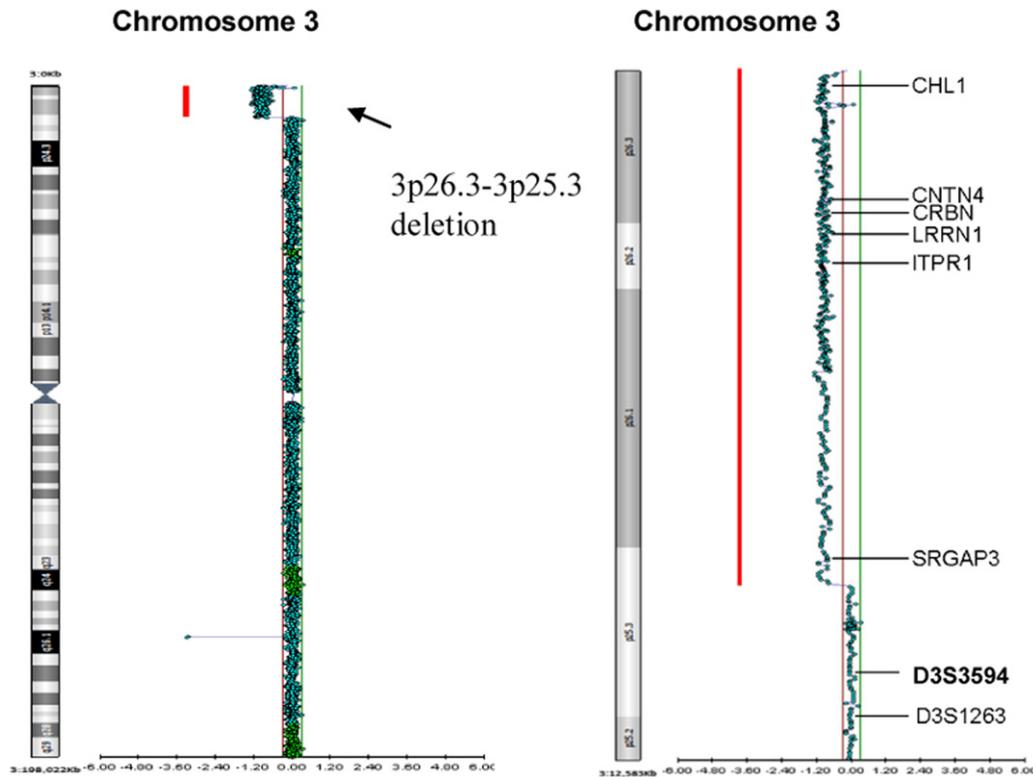


Fig. 1. Array comparative genomic hybridization investigation shows an ~ 9.29-Mb deletion of 3p25.3 → pter encompassing the genes of *CHL1*, *CNTN4*, *CRBN*, *LRRN1*, *ITPR1*, and *SRGAP3* but without involvement of the markers D3S1263 and D3S3594.

mental retardation, developmental delay, intrauterine growth restriction, micro- and brachycephaly, a triangular face, hypertelorism, epicanthus, upturned palpebral fissures, palpebral ptosis, frontal bossing, a short and thick nose, micrognathia, low-set ears, hypertrichosis, synophrys, long philtrum, and variable associated abnormalities, such as pectus excavatum, scoliosis, hypogenitalia, polydactyly, syndactyly, clinodactyly, atrioventricular septal defects, hiatal hernia, optic atrophy, polycystic renal dysplasia, and hypoplastic clavicles [1–4]. Here, we present our experience of prenatal diagnosis and array comparative genomic hybridization (aCGH) characterization of pure partial monosomy 3p (3p25.3 → pter) in a fetus.

### Case report

A 35-year-old, gravida 2, para 0, woman underwent amniocentesis at 19 weeks of gestation because of advanced maternal age. Her husband was 37 years of age. She had experienced one intrauterine fetal death. Amniocentesis during this pregnancy revealed a distal deletion of chromosome 3p. The parental karyotypes were normal. Prenatal ultrasonography findings were unremarkable. At 22 weeks of gestation, she underwent repeated amniocentesis, and aCGH investigation using CytoChip Oligo Array (BlueGnome, Cambridge, UK) on uncultured amniocytes revealed a 9.29-Mb deletion of 3p26.3p25.3 [arr 3p26.3p25.3 (64,096–9,357,258 bp) ×1] encompassing the genes of *CHL1*, *CNTN4*, *CRBN*, *LRRN1*,

*ITPR1*, and *SRGAP3* (Fig. 1). Polymorphic DNA marker analysis on uncultured amniocytes showed a paternal origin of the deletion (Fig. 2, Table 1). Cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XX,del(3)(p25.3; Fig. 3). At 24 weeks of gestation, prenatal ultrasonography

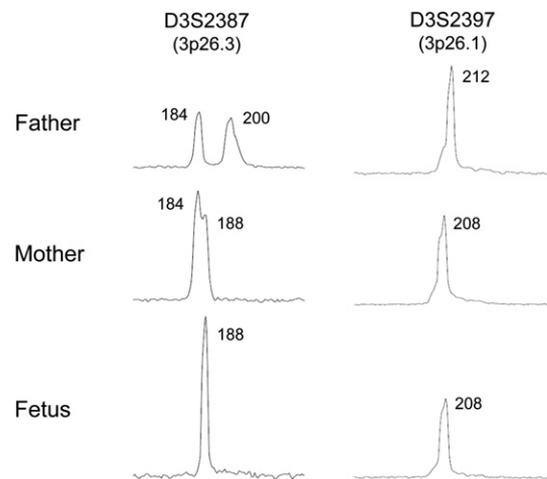


Fig. 2. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays at short tandem repeat markers specific for chromosome 3p using uncultured amniocytes and parental DNAs. With the marker D3S2387 (3p26.3), only the allele of 188 bp (maternal) is present in the fetus. With the marker D3S2397 (3p26.1), only the allele of 208 bp (maternal) is present in the fetus. The results indicate a paternal origin of the deletion.

Table 1  
Molecular results using polymorphic DNA markers specific for chromosome 3p.<sup>a</sup>

Markers	Locus	Father	Mother	Fetus (uncultured amniocytes)
D3S2387	3p26.3	184, 200	184, 188	188
D3S2397	3p26.1	212, 212	208, 208	208
D3S2385	3p25.1	155, 155	147, 151	147, 155

<sup>a</sup> Alleles (basepair sizes) are listed below each individual.

findings of the brain, heart, and other internal organs were unremarkable. The pregnancy was subsequently terminated, and an 886-g female fetus was delivered with brachycephaly, hypertelorism, a short and thick nose, micrognathia, and low-set ears (Fig. 4).

## Discussion

The present case was not associated with congenital heart disease (CHD). The deleted segment of chromosome 3p in this case did not involve the candidate CHD critical region associated with the 3p deletion syndrome. Green et al [5] mapped the 3p25 CHD susceptibility locus to a 3.7 cM distance between D3S1263 (11,492,252–11,492,482 bp) and D3S3594 (10,626,638–10,626,908 bp). Shuib et al [4] additionally mapped the 3p25 CHD susceptibility locus to an ~ 200 kb interval between the deletion size of 11.35 Mb (with CHD) and the deletion size of 11.15 Mb (without CHD) by analysis of cases with a deletion of 3p25.3-pter. The present case had a deletion size about 9.35 Mb, and it is likely that a CHD susceptibility gene was not involved within this deletion.

The present case had haploinsufficiency of the neurodevelopmental genes of *CHLI*, *CNTN4*, *CRBN*, *LRRN1*,

*ITPR1*, and *SRGAP3*. *CHLI* (OMIM 607416) encodes cell adhesion molecule L1-like (CALL) protein. CALL is highly expressed in the central nervous system and the peripheral nervous system, and interruption or loss of CALL may cause cognitive deficit [6,7]. In a study of genotype-phenotype correlation of terminal 3p deletions in two families, Pohjola et al [8] concluded that a small terminal 3p deletion encompassing only the *CHLI* gene may cause only mild mental deficit, mild learning difficulty, microcephaly and growth retardation, but may not be related to profound mental retardation and dysmorphisms.

*CNTN4* (OMIM 607280) encodes contactin 4 that belongs to an axon-associated cell adhesion molecule of immunoglobulin superfamily and plays a role in the formation, maintenance and plasticity of functional neuronal networks [9,10]. Dijkhuizen et al [11] suggested that loss of *CNTN4* and *CRBN* contributes to mental retardation in the 3p deletion syndrome. Fernandez et al [12,13] suggested that disruption or haploinsufficiency of *CNTN4* causes characteristic physical features of the 3p deletion syndrome including developmental delay, dysmorphic features and growth retardation.

*CRBN* (OMIM 609262) encodes cereblon that is a binding protein for large-conductance calcium-activated potassium channel in the brain [14]. Autosomal recessive nonsyndromic mental retardation-2 (MRT2) (OMIM 607417) can be caused by homozygous mutation in *CRBN* [15–17]. *LRRN1* is required for formation of the midbrain-hindbrain boundary during neuronal development [18,19]. *ITPR1* (OMIM 147265) encodes inositol 1,4,5-trisphosphate receptor type 1, which releases calcium ions from intracellular stores and modulates intracellular calcium signaling [20]. Cargile et al [21] suggested that *ITPR1* is a candidate gene for mental retardation in the 3p deletion syndrome.



Fig. 3. A karyotype of 46,XX,del(3)(p25.3). The arrow indicates the breakpoint.



Fig. 4. The fetus at birth.

*SRGAP3* (OMIM 606525) encodes Slit-Robo Rho GTPase-activating protein 3, which is involved in the Slit-Robo pathway regulating neuronal migration and axonal branching. Endris et al [22] reported a patient with a balanced *de novo* translocation t(X;3)(p11.2;p25) with hypotonia and severe mental retardation. Endris et al [22] found that the chromosome breakpoint interrupted the *SRGAP3* gene in their patient with the 3p deletion syndrome and suggested that haploinsufficiency of *SRGAP3* may lead to misregeneration of neuronal signal transduction and abnormal development of neuronal structures. Shuib et al [4] analyzed 14 patients with cytogenetically detectable deletions of 3p25 and mapped a candidate critical region for mental retardation to an ~ 1 Mb interval containing only *SRGAP3* rather than *CHL1*, *CNTN4*, *CRBN*, and *ITPR1*. Shuib et al [4] suggested that *SRGAP3* is a major determinant of mental retardation in the 3p deletion syndrome.

In conclusion, we present prenatal diagnosis and aCGH characterization of pure partial monosomy 3p (3p25.3 → pter) in a fetus with haploinsufficiency of a candidate critical region for cognitive deficit and mental retardation in the 3p deletion syndrome. In this case, aCGH has characterized a 3p-deleted region with involvement of the neurodevelopmental genes of *CHL1*, *CNTN4*, *CRBN*, *LRRN1*, *ITPR1*, and *SRGAP3* but without involvement of the CHD susceptibility locus, and QF-PCR has determined a paternal origin of the deletion. aCGH and QF-PCR help to delineate the genomic imbalance in prenatally detected *de novo* chromosome aberration, and the information acquired is useful for genetic counseling.

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#### References

- [1] Chen C-P, Liu F-F, Jan S-W, Lin S-P, Lan C-C. Prenatal diagnosis of partial monosomy 3p and partial trisomy 2p in a fetus associated with shortening of long bones and a single umbilical artery. *Prenat Diagn* 1996;16:270–5.
- [2] Chen C-P, Lin S-P, Ho C-S, Chern S-R, Lee C-C, Chen W-L, et al. Distal 3p monosomy associated with epilepsy in a boy. *Genet Counsel* 2005;16:429–32.
- [3] Chen C-P, Su Y-N, Hsu C-Y, Chern S-R, Lee C-C, Chen Y-T, et al. Mosaic deletion-duplication syndrome of chromosome 3: prenatal molecular cytogenetic diagnosis using cultured and uncultured amniocytes and association with fetoplacental discrepancy. *Taiwan J Obstet Gynecol* 2011;50:485–91.
- [4] Shuib S, McMullan D, Rattenberry E, Barber RM, Rahman F, Zatyka M, et al. Microarray based analysis of 3p25-p26 deletions (3p- syndrome). *Am J Med Genet* 2009;149A:2099–105.
- [5] Green EK, Priestly MD, Waters J, Maliszewska C, Latif F, Maher ER. Detailed mapping of a congenital heart disease gene in chromosome 3p25. *J Med Genet* 2000;37:581–7.
- [6] Frints S, Marynen P, Hartmann D, Fryns J, Steyaert J, Schachner M, et al. *CALL* interrupted in a patient with non-specific mental retardation: gene dosage-dependent alteration of murine brain development and behavior. *Hum Mol Genet* 2003;12:1463–74.
- [7] Shrimpton A, Jensen K, Hoo J. Karyotype-phenotype analysis and molecular delineation of a 3p26 deletion/8q24.3 duplication case with a virtually normal phenotype and mild cognitive deficit. *Am J Med Genet* 2006;140A:388–91.
- [8] Pohjola P, De Leeuw N, Penttinen M, Kääriäinen H. Terminal 3p deletions in two families – correlation between molecular karyotype and phenotype. *Am J Med Genet* 2010;152A:441–6.
- [9] Yoshihara Y, Kawasaki M, Tamada A, Nagata S, Kagamiyama H, Mori K. Overlapping and differential expression of BIG-2, BIG-1, TAG-1, and F3: four members of an axon-associated cell adhesion molecule subgroup of the immunoglobulin superfamily. *J Neurobiol* 1995;28:51–69.
- [10] Saito H, Mimmack M, Kishimoto J, Keverne EB, Emson PC. Expression of olfactory receptors, G-proteins and AxCAMs during the development and maturation of olfactory sensory neurons in the mouse. *Dev Brain Res* 1998;110:69–81.
- [11] Dijkhuizen T, Van Essen T, Van Der Vlies P, Verheij J, Sikkema-Raddatz B, Van Der Veen A, et al. FISH and array-CGH analysis of a complex chromosome 3 aberration suggests that loss of *CNTN4* and *CRBN* contributes to mental retardation in 3pter deletions. *Am J Med Genet* 2006;140A:2482–7.

- [12] Fernandez T, Morgan T, Davis N, Klin A, Morris A, Farhi A, et al. Disruption of contactin 4 (*CNTN4*) results in developmental delay and other features of 3p deletion syndrome. *Am J Hum Genet* 2004;74: 1286–93.
- [13] Fernandez TV, García-González IJ, Mason CE, Hernández-Zaragoza G, Ledezma-Rodríguez VC, Anguiano-Alvarez VM, et al. Molecular characterization of a patient with 3p deletion syndrome and a review of the literature. *Am J Med Genet* 2008;146A:2746–52.
- [14] Jo S, Lee K-H, Song S, Jung Y-K, Park C- S. Identification and functional characterization of cereblon as a binding protein for large-conductance calcium-activated potassium channel in rat brain. *J Neurochem* 2005; 94:1212–24.
- [15] Higgins JJ, Rosen DR, Loveless JM, Clyman JC, Grau MJ. A gene for nonsyndromic mental retardation maps to chromosome 3p25-pter. *Neurology* 2000;55:335–40.
- [16] Higgins JJ, Pucilowska J, Lombardi RQ, Rooney JP. A mutation in a novel ATP-dependent Lon protease gene in a kindred with mild mental retardation. *Neurology* 2004;63:1927–31.
- [17] Higgins JJ, Hao J, Kosofsky BE, Rajadhyaksha AM. Dysregulation of large-conductance  $Ca^{2+}$ -activated  $K^{+}$  channel expression in nonsyndromal mental retardation due to a cereblon p.R419X mutation. *Neurogenetics* 2008;9:219–23.
- [18] Andrae LC, Peukert D, Lumsden A, Gilthorpe JD. Analysis of *Lrrn1* expression and its relationship to neuromeric boundaries during chick neural development. *Neural Dev* 2007;2:22.
- [19] Tossell K, Andrae LC, Cudmore C, Lang E, Muthukrishnan U, Lumsden A, et al. *Lrrn1* is required for formation of the midbrain-hindbrain boundary and organiser through regulation of affinity differences between midbrain and hindbrain cells in chick. *Dev Biol* 2011;352: 341–52.
- [20] Berridge MJ. Inositol trisphosphate and calcium signalling. *Nature* 1993; 361:315–25.
- [21] Cargile CB, Goh DL-M, Goodman BK, Chen XN, Korenberg JR, Semenza GL, et al. Molecular cytogenetic characterization of a subtle interstitial del(3)(p25.3p26.2) in a patient with deletion 3p syndrome. *Am J Med Genet* 2002;109:133–8.
- [22] Endris V, Wogatzky B, Leimer U, Bartsch D, Zatyka M, Latif F, et al. The novel Rho-GTPase activating gene *MEGAP/srGAP3* has a putative role in severe mental retardation. *Proc Nat Acad Sci U S A* 2002;99: 11754–9.