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Short Communication

Mosaic deletion-duplication syndrome of chromosome 3: Prenatal molecular cytogenetic diagnosis using cultured and uncultured amniocytes and association with fetoplacental discrepancy

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Abstract

Objective: To present prenatal molecular cytogenetic diagnosis of mosaicism for terminal 3p deletion and distal 3q duplication using cultured and uncultured amniocytes, and the association with fetoplacental discrepancy.

Materials, Methods, and Results: A 35-year-old primigravid woman was referred for genetic counseling at 21 weeks of gestation because of 20% (5/25 colonies) mosaicism for add(3)(p26) detected by amniocentesis. Repeated amniocenteses were performed. Array comparative genomic hybridization (aCGH) and interphase fluorescence *in situ* hybridization (FISH) were applied in the uncultured amniocytes. aCGH analysis detected 0.15-Mb microdeletion of 3p26.3 with *CHL1* haploinsufficiency and a 49.42-Mb duplication of 3q24-q29 in the uncultured amniocytes. Interphase FISH analysis revealed 27.3% mosaicism (12/44 cells) in the uncultured amniocytes. Metaphase FISH analysis revealed 23.3% mosaicism (7/30 cells) in the cultured amniocytes. Conventional cytogenetic analysis showed a karyotype of 46,XX,der(3)(qter → q24::p26.3 → qter)[10]/46,XX[20] (33% mosaicism). Subsequent fetal blood sampling showed a karyotype of 46,XX,der(3)(qter → q24::p26.3 → qter)[5]/46,XX[35] (12.5% mosaicism). The parents elected to terminate the pregnancy, and a malformed fetus was delivered at 24 weeks of gestation with characteristic facial dysmorphism and clinodactyly of the hands. Cytogenetic analysis of the extra-embryonic tissues revealed the results of 46,XX (40 cells) in placenta, 25% mosaicism (10/40 cells) in amniotic membrane and 50% mosaicism (20/40 cells) in umbilical cord.

Conclusion: Our presentation highlights the utility of molecular cytogenetic technologies in prenatal diagnosis of rare mosaic chromosome rearrangements and provides evidence for fetoplacental discrepancy under such circumstances.

Keywords: 3p deletion; 3q duplication; *CHL1*; Deletion-duplication syndrome of chromosome 3; Fetoplacental discrepancy; Mosaicism

Introduction

The deletion-duplication syndrome of chromosome 3 consists of partial 3p deletion and partial 3q duplication. Both 3p deletion syndrome and 3q duplication syndrome are rare but clinically recognizable chromosome abnormalities.

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Clinical reports with deletion-duplication syndrome of chromosome 3 resulting from familial pericentric inversions of chromosome 3 have been well described. Most cases resulted from a pericentric inversion with breakpoints at 3p and 3q in the parents. These cases include dup(3)(q21 → qter) & del(3)(pter → p25) [1–5], dup(3)(q23 → qter) & del(3)(pter → p25) [6–9] and dup(3)(q25 → qter) & del(3)(pter → p25) [10–12].

Prabhakara et al. [13] first reported prenatal diagnosis of deletion-duplication syndrome of chromosome 3 in a fetus with lumbosacral meningocele, a karyotype of 46,XY,add(3)(p26) and a familial pericentric inversion of 46,XY,inv(3)(p26q21) in the father. In that case, molecular cytogenetic investigations revealed dup(3)(q21 → qter) & del(3)(pter → p26.1) in the fetus. Prenatal diagnosis of mosaic deletion-duplication syndrome of chromosome 3 has not previously been described. Here, we present such a case in which a cytogenetic discrepancy between the fetus and the placenta was noted. Our presentation highlights the utility of high-resolution molecular cytogenetic technologies in prenatal diagnosis of mosaic chromosome rearrangements using both cultured and uncultured amniocytes.

Materials, methods and results

A 35-year-old primigravid woman was referred for genetic counseling at 21 weeks of gestation because of an abnormal amniocentesis result of mosaicism for a derivative chromosome 3 of add(3)(p26). She had undergone amniocentesis at 20 weeks of gestation in an obstetric clinic because of advanced maternal age. Amniocentesis revealed a karyotype of 46,XX,add(3)(p26)[5 colonies]/46,XX[20 colonies]. Among 25 colonies of cultured amniocytes, five colonies had a derivative chromosome 3 [der(3)], of which additional maternal was attached to band 3p26, whereas the other 20 colonies had a normal karyotype. Repeated amniocentesis was performed at 21 weeks of gestation. Oligonucleotide-based array comparative genomic hybridization (aCGH) using CytoChip Oligo Array (BlueGnome, Cambridge, UK) and interphase fluorescence *in situ* hybridization (FISH) were applied in the uncultured amniocytes. The aCGH analysis rapidly detected gene dosage decrease at 3p26.3 and gene dosage increase at 3q24-q29 in the uncultured amniocytes (Fig. 1A). There were a 0.15-Mb microdeletion of 3p26.3 (134,741–287,068 bp) and a 49.42-Mb duplication of 3q24-q29 (149,900,377–199,321,417 bp) (Fig. 1B) [UCSC genome browser on March 2006 (NCBI 36/hg 18) assembly].

The interphase FISH analysis using chromosome 3p- and 3q-specific bacterial artificial chromosome (BAC) clone probes RP11-210M17 (3p26.3: 129,717–287,700 bp) (spectrum red) and RP11-338O10 (3q29: 195,287,280–195,356,374 bp) (spectrum green) revealed 27.3% (12/44) mosaicism for the der(3). Among 44 interphase uncultured amniocytes analyzed, 12 cells (27.3%) showed three green signals and one red signal

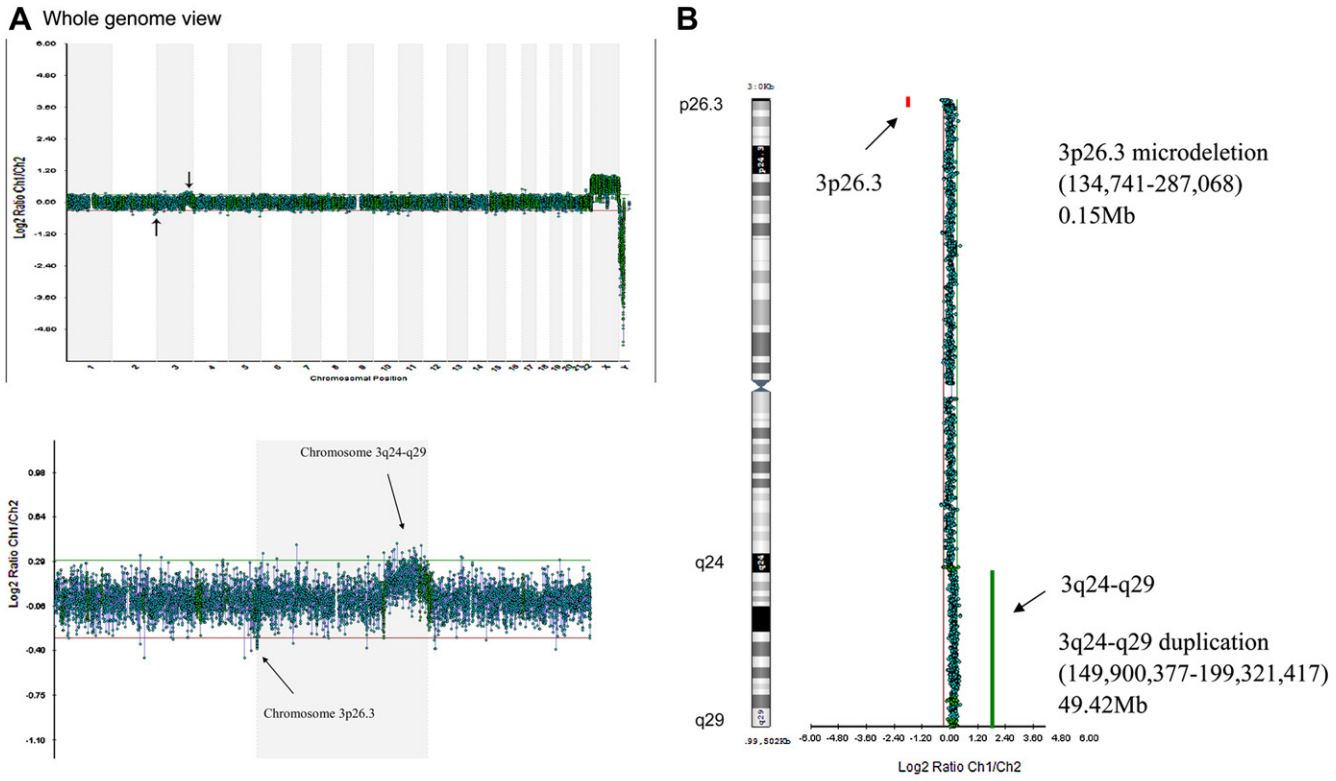

Fig. 1. (A) Oligonucleotide-based array comparative genomic hybridization (aCGH) using CytoChip Oligo Array (BlueGnome, Cambridge, UK) in uncultured amniocytes shows gene dosage decrease at 3p26.3 and gene dosage increase at 3q24-q29 (arrows). (B) aCGH shows a 0.15-Mb microdeletion of 3p26.3 (134,741–287,068 bp) and a 49.42-Mb duplication of 3q24-q29 (149,900,377–199,321,417 bp).

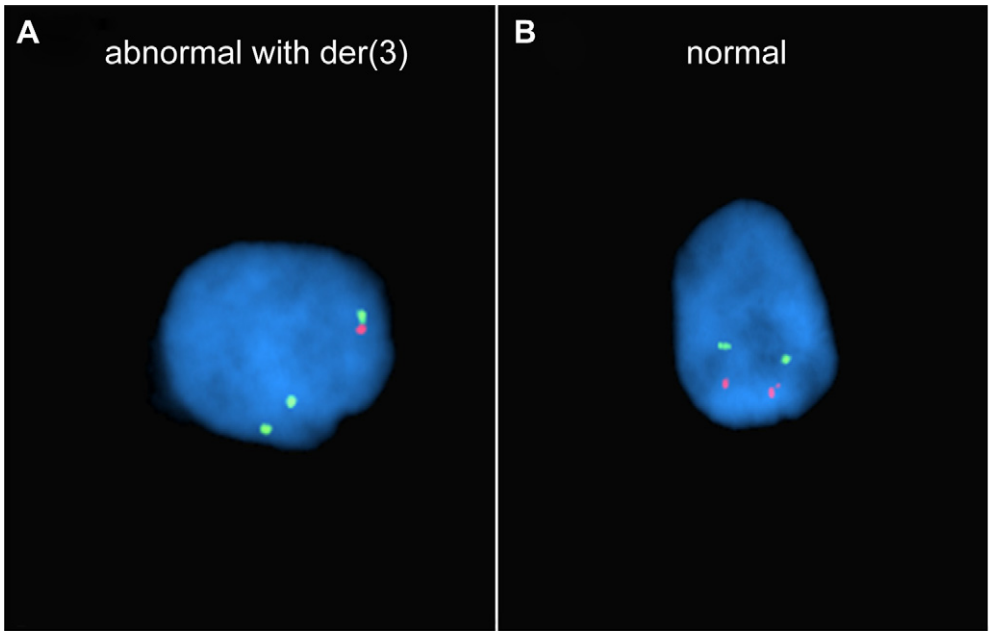

Fig. 2. Interphase fluorescence *in situ* hybridization (FISH) analysis using bacterial artificial chromosome (BAC) clone probes RP11-210M17 (3p26.3: 129,717–287,700 bp) (spectrum red) and RP11-338O10 (3q29: 195,287,280–195,356,374 bp) (spectrum green) shows (A) three green signals and one red signal in the abnormal uncultured amniocytes with a derivative chromosome 3 [der(3)], and (B) two red signals and two green signals in the normal uncultured amniocytes.

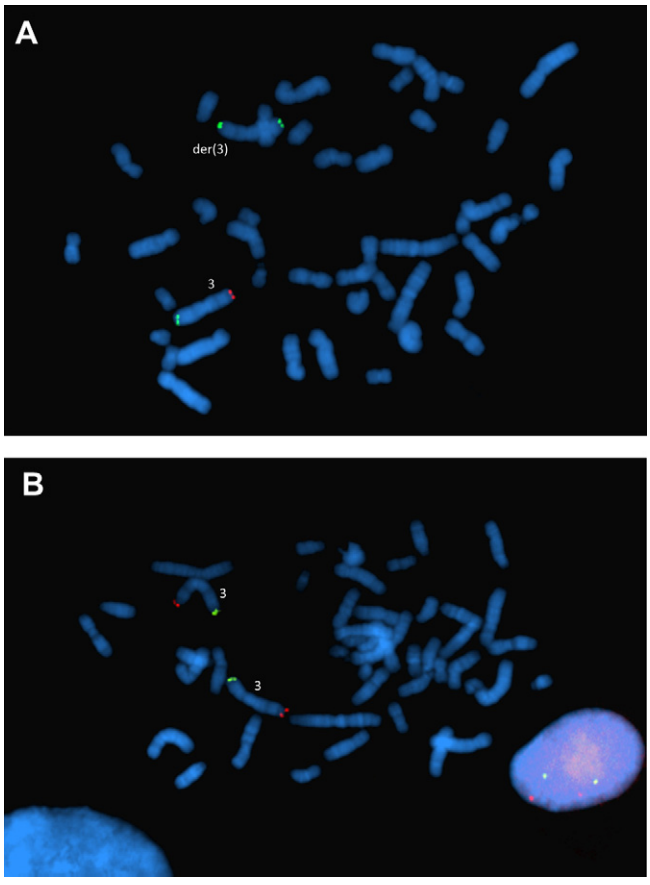

Fig. 3. Metaphase FISH analysis of cultured amniocytes using BAC clone probes RP11-210M17 and RP11-338O10 shows (A) an abnormal amniocyte with a normal chromosome 3 containing one green signal and one red signal, and a der(3) containing two green signals, and (B) a normal amniocyte with two normal chromosomes 3.

consistent with the diagnosis of 3q duplication and 3p deletion, whereas the other 32 cells were normal (Fig. 2). The metaphase FISH analysis of cultured amniocytes using BAC clone probes RP11-210M17 and RP11-338O10 revealed 23.3% (7/30)

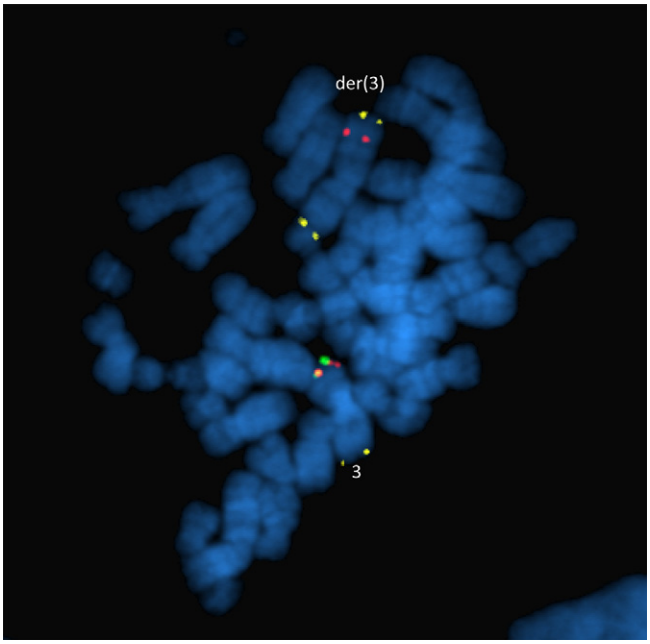

Fig. 4. Metaphase FISH analysis of the abnormal cultured amniocytes using BAC clone probes RP11-306H5 (spectrum green) (3p26.3, encompassing *CHL1* gene), RP11-129K1 (spectrum red) (3p26.3, encompassing *CNTN4* gene) and RP11-338O10 (spectrum yellow) (3q29) shows a normal chromosome 3 containing one green signal, one red signal and one yellow signal, and a der(3) containing two yellow signals and one red signal. The result indicates *CHL1* haploinsufficiency but presence of the *CNTN4* gene in the der(3).

mosaicism for the derivative chromosome 3 (Fig. 3). The metaphase FISH analysis of the abnormal cultured amniocytes using BAC clone probes RP11-306H5 (3p26.3: 325,397–326,005 bp) (spectrum green) encompassing *CHL1* gene, RP11-129K1 (3p26.3: 2,215,034–2,377,366 bp) (spectrum red) encompassing *CNTN4* gene and RP11-338O10 (spectrum yellow) (3q29) showed *CHL1* haploinsufficiency but presence of the *CNTN4* gene in the der(3) (Fig. 4). Among 30 metaphase cultured amniocytes analyzed, seven cells (23.3%) showed 3p deletion and 3q duplication, whereas the other 23 cells were normal. Conventional cytogenetic analysis showed a karyotype of 46,XX,der(3)(qter → q24::p26.3 → qter)[10 colonies]/46,XX[20 colonies] (33% mosaicism) (Fig. 5).

Prenatal ultrasound findings were unremarkable. Subsequent fetal blood sampling showed a karyotype of 46,XX,der(3)(qter → q24::p26.3 → qter)[5 cells]/46,XX[35 cells] (12.5% mosaicism). The parents elected to terminate the pregnancy, and a 616-g female fetus was delivered at 24 weeks of gestation with a triangular face, hypertelorism, depressed nasal bridge, anteverted nostrils, long philtrum, down-turned mouth, low-set ears and clinodactyly of the hands (Fig. 6). Cytogenetic analysis of the extraembryonic tissues revealed the results of 46,XX[40 cells] in placenta, 46,XX,der(3)(qter → q24::p26.3 → qter)[10 cells]/46,XX[30 cells] (25% mosaicism) in amniotic membrane and 46,XX,der(3)(qter → q24::p26.3 → qter)[20 cells]/46,XX[20 cells] (50%

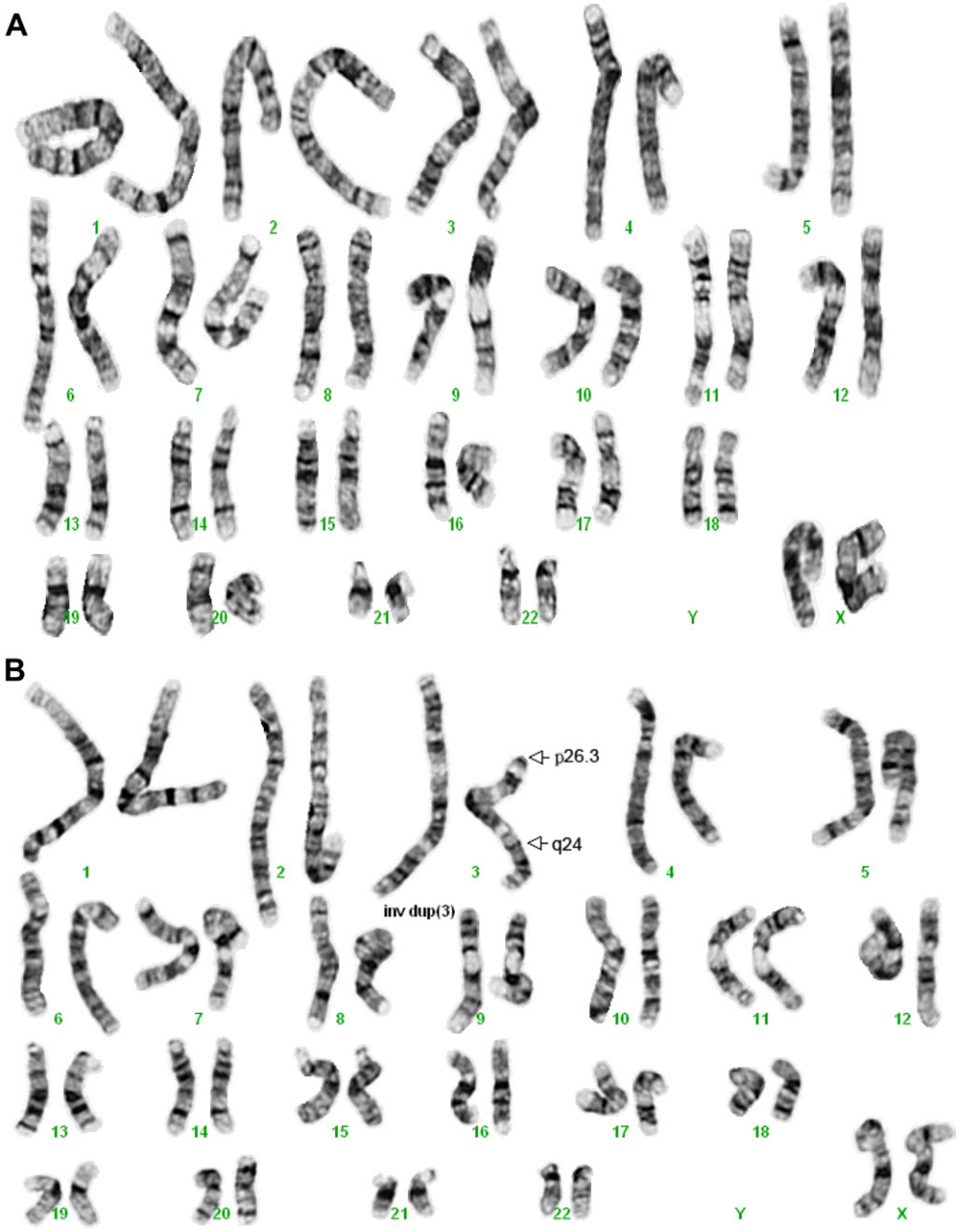

Fig. 5. (A) A karyotype of 46,XX. (B) A karyotype of 46,XX,der(3)(qter → q24::p26.3 → qter).

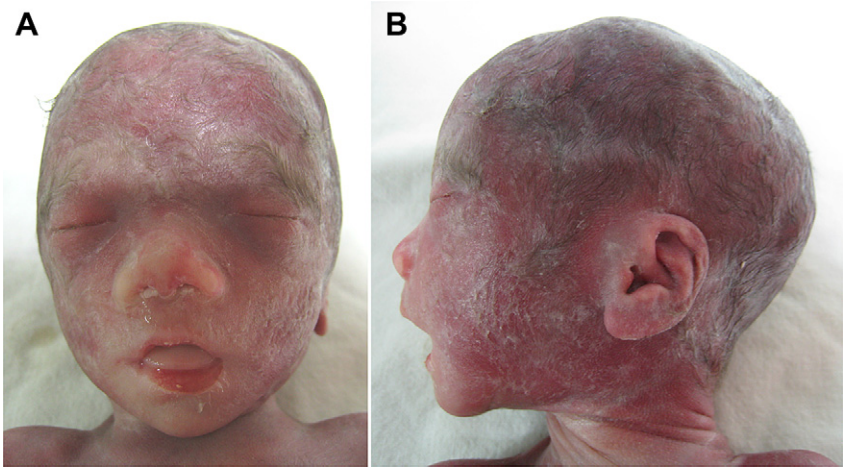

Fig. 6. (A) and (B) Craniofacial appearance of the fetus at birth.

mosaicism) in umbilical cord. Polymorphic DNA marker analysis excluded uniparental disomy 3.

Discussion

Prabhakara et al. [13] first reported prenatal diagnosis of a malformed fetus with deletion-duplication of chromosome 3 arising from meiotic recombination of a familial pericentric inversion. In a literature review of patients with partial 3q duplication and partial 3p deletion, Steinbach et al. [12] suggested that deletion-duplication of chromosome 3 is a result of meiotic recombination. The presence of a normal cell line in our case is consistent with the postzygotic origin of the recombinant chromosome 3 in the fetus, and provides evidence that deletion-duplication of chromosome 3 can present in a mosaic form and arise from a postzygotic mitotic event.

The present case demonstrates a fetoplacental discrepancy in mosaic deletion-duplication syndrome of chromosome 3, and shows a limitation of using placenta as a diagnostic tool for prenatal diagnosis of mosaic chromosome rearrangements. Our case reinforces the notion that amniocentesis offers a more reliable diagnosis of chromosome aberrations compared to chorionic villus sampling.

The present case shows that oligonucleotide-based aCGH using CytoChip Oligo Array is able to detect genomic imbalance in uncultured amniocytes with 27.3% (12/44) mosaicism for terminal 3p deletion and distal 3q duplication. We previously demonstrated that BAC-based aCGH using CMDX BAC aCGH 2500 Chips was not able to detect genomic imbalance in uncultured amniocytes with 18% (9/50) mosaicism for trisomy 9 [14], and aCGH using CMDX BAC aCGH 3000 Chips and Oligo HD Scan (CMDX, Irvine, CA, USA) was not able to detect genomic imbalance in uncultured amniocytes with 25% (5/20) mosaicism for trisomy 8 [15]. We previously also demonstrated that CytoChip Oligo Array (BlueGnome, Cambridge, UK) was able to detect genomic imbalance in uncultured amniocytes with 12% (6/50) mosaicism for trisomy 2 [16]. It is likely that variation in the ability of detection of low-level mosaicism in uncultured amniocytes exists in different commercial kits of aCGH.

The 3p deletion syndrome is a rare contiguous gene syndrome involving chromosome 3p25-p26 deletion and is characterized by low birth weight, psychomotor delay, growth retardation and characteristic facial dysmorphism of micro- and brachycephaly, flat occiput, triangular face, hypertelorism, epicanthic folds, ptosis, broad and short nose, long philtrum, down-turned mouth, micrognathia, low-set ears, hypertrichosis and synophrys [17–21]. Fernandez et al. [22] suggested that *CNTN4* disruption is associated with 3p deletion syndrome phenotype and abnormal central nervous system development. Dijkhuizen et al. [23] suggested that loss of *CNTN4* and *CRBN* contributes to mental retardation in 3p deletion syndrome. There was no loss of the genes of *CNTN4* and *CRBN* in this case. The 3p deletion in this case encompassed only a 0.15-Mb region of terminal 3p26.3 overlapping part of the *CHL1* gene (213,650–426,097 bp). The *CHL1* gene encodes cell adhesion molecule L1-like (CALL or CAL1) protein which is highly expressed in central and peripheral nervous system [24,25]. Frints et al. [25] and Shrimpton et al. [26] suggested that interruption or loss of the *CHL1* gene may cause cognitive deficit. Pohjola et al. [27] recently reported a family with a 1.1-Mb terminal 3p deletion encompassing only the *CHL1* gene and was associated with nonspecific features, mild learning difficulty, microcephaly and growth retardation. They suggested that a small terminal deletion comprising only the *CHL1* gene may not be related to dysmorphic features and profound mental retardation but may cause only a mild mental deficit.

The 3q duplication syndrome is a well-described chromosome disorder that has the clinical overlap with Cornelia de Lange syndrome, such as developmental delay, failure to thrive, low anterior hairline, prominent eyelashes, depressed nasal bridge, anteverted nares, long prominent philtrum, micrognathia, rhizomelic shortening of the limbs and genital hypoplasia; and other features such as normal birth weight, bushy eyebrows, ocular hypertelorism, up-slanting palpebral fissures, epicanthic folds, a broad nose and normal lips [28].

Partial duplication of 3q can be associated with major congenital malformations, such as omphalocele [6,29−34], cystic hygroma [35,36], holoprosencephaly [37], spina bifida or sacral dimple [3], lumbosacral meningocele [13], Dandy-Walker malformation [38], and cerebellar hypoplasia and agenesis of the corpus callosum [39]. The minimal critical region for most of the clinical features of 3q duplication syndrome has been narrowed down to 3q26.3-q29 [40−45]. The 3q duplication in this case encompassed a 49.42-Mb duplication of 3q24-q29 overlapping the critical region of 3q duplication syndrome, and was associated with characteristic craniofacial dysmorphism of 3q duplication syndrome.

In conclusion, by using FISH and aCGH in cultured and uncultured amniocytes, we are able to precisely define a mosaic chromosome rearrangement in a fetus with concomitant 3p deletion syndrome and 3q duplication syndrome. Our presentation highlights the utility of molecular cytogenetic technologies in prenatally detected rare mosaic chromosome rearrangements and provides evidence for feto-placental discrepancy under such circumstances.

Acknowledgments

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