A new case of interstitial 1q 25.3-32.1 deletion: cytogenetic analysis molecular characterization and ultrasound findings

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Abstract

Introduction: deletion of long arm of chromosome 1(1q-) is a rare condition. Clinical features include Dwarfism, severe mental retardation, microcephaly and short neck delineating the “intermediate 1q deletion syndrome”.

Case Report: we report a new case of interstitial deletion of the long arm of chromosome 1, diagnosed in a 22+3 weeks gestation fetus in which cytogenetic analysis localized a loss of genetic materials of 18Mb in the 1q25.3-32.1. Fetal ultrasound showed neurodegenerative defects resembling Dandy-Walker's syndrome and bilateral clubfoot.

Conclusions: clinical characteristics of our case are markedly mild. This suggests that the type and the extension of the mutation obtained

through cytogenetic studies, CGH array and ultrasound evaluation should be taken into account for prognostic evaluation and management of these patients.

Key words: chromosome 1; interstitial deletion; intermediate 1q deletion syndrome; Dandy-Walker; bilateral clubfoot.

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The Authors attest that they have obtained written consent from the patient.

Introduction

Deletions of the long arm of chromosome 1 are relatively rare conditions and not inherited in the majority of cases. The size of the deletions and the resulting phenotype varies among patients. However, some features are common among patients as the chromosomal regions included in the deletions.

In the past, the deletion patients have been classified into three groups based on the region of monosomy; 1q21-q25, 1q25-q32 and 1q42qter (1). Recently the lack of corresponding phenotypes has led to the definition of a unique “interstitial 1q deletion syndrome”, even if, the classification proposed by Taysi et al. (2), in proximal and intermediate deletion involving 1q21-22 [arrow right] q25 and 1q24-25 [arrow right] q32 chromosome regions, respectively, is more suitable for classic cytogenetic studies. 32 cases of 1q interstitial deletion have been described within literature, most of which have been diagnosed in patients with milder or severe clinical features (1, 3): cryptorchidism, micrognathia, abnormally modelled ears, delayed speech development (1), dwarfism mental retardation, microcephaly (4) and malformations of many organs (5). To date, only very few cases of terminal 1q deletion syndrome have been diagnosed in utero, mainly after 20 weeks of gestation.

In the present case, we described, a *de novo* interstitial deletion involving 1q 25.3-32.1 chromosome bands, revealed by cytogenetic analysis and array-CGH, in a fetus at 22+3 weeks gestation.

Case Report

A 29-year-old pregnant woman at 22+3 weeks of gestation underwent to routine ultrasound examinations in our institute. This was her first pregnancy (gravida

Figure 1. Microarray plot for a *de novo* clinically significant 18 Mb deletion at 1q 25.3-32.1.

1, para 0) and no previous medical or obstetrical history was recorded. The pregnancy had been conceived spontaneously and any significant signs of anomaly had not been revealed until that point. Family history didn't reveal genetic diseases and prospective parents were both apparently healthy. Ultrasonography revealed a single live intra-uterine gestation with biparietal diameter and foetal femur length corresponding to 22 weeks of gestation. The amniotic fluid was regular. The foetal posterior fossa was of normal size but with a small anechoic lesion which was communicating with the 4th ventricle. There was a suggestion of hypoplasia of the cerebellar vermis but no evidence of hydrocephalus. There was no sonographic evidence of agenesis of the corpus callosum or any other congenital intracranial malformation. The bones of the foot appeared to be in the same planes as the bones of the lower leg and this abnormality was bilateral.

In conclusion, ultrasound examination suggested borderline neurodegenerative defects resembling Dandy-Walker's syndrome and bilateral clubfoot, therefore amniocentesis was performed.

Cytogenetic Studies

Cytogenetic analysis were carried out on chromosome spreads prepared from three independent primary amniocytes cultures. After staining with the trypsin-Giemsa banding technique a total of 16 metaphases were analyzed. Analysis of peripheral lymphocytes of parental chromosomes showed normal karyotypes.

Array-Comparative Genomic Hybridization (CGH)

Array-CGH analysis was tested on patient's DNA, extracted from amniotic fluid cells. The genomic coverage of these arrays is up to 1Mb resolution across the genome and ~100 kb resolution in 139 regions associated with constitutional disorders. DNA was hybridized to whole-genome BAC microarrays (Bacterial Artificial Chromosomes) – CytoChip FocusConstitutional (BlueGnome, Cambridge, UK), according to the manufacturer's protocol (available at www.cytochip.com). A laser scanner InnoScan 710 AL (INNOPSYS, Carbonne, France) was used to excite the hybridized fluorophores, read and store the resulting images of the hybridization. Scanned image quantification, array quality control and aberration detection were performed by algorithm fixed settings in BLUEFUSE MULTI software (BlueGnome, Cambridge, UK) (4).

G banding karyotype analysis showed an interstitial deletion of the long arm of chromosome 1, 46,del (1) (q25→q32) and the parents' karyotypes were normal. About 18 Mb in the chromosomal region were identified using BAC array CGH analysis (Fig. 1).

Outcome

The patient was followed up till her delivery and no additional findings were detected in the subsequent ultrasound examinations.

Spontaneous delivery occurred at term of gestation. Birth weight was 2750 g. Physical examination showed dysmorphic features including a wide and receding forehead, broad nasal bridge, redundant retro-nuchal skin, low set and poorly shaped ears. Cranial

ultrasound done immediately after birth revealed an anechoic posterior fossa mass lesion communicating with the 4th ventricle with no evidence of vermian hypoplasia. There was no sonographic evidence of agenesis of the corpus callosum or any other congenital intracranial malformation. Abdominal ultrasound revealed no abnormalities. Echocardiography of the baby showed absence of any congenital cardiac defects. The prenatal ultrasound diagnosis of clubfoot was confirmed. At 24 hours from birth, he was admitted to a neonatal care unit because of respiratory distress.

Discussion

Few reports of interstitial deletions of the long arm of chromosome 1 have been published. Phenotypic characteristics including typical facial appearance, microcephaly, psychomotor retardation and variable other anomalies are suggested to be based on the loss of macrochromosomal materials within the long arm of chromosome 1. The number of symptoms is related to the loss of genetic material (6).

We have found a *de novo* interstitial deletion spanning chromosome 1q 25.3-32.1 in a 22+3 weeks gestation fetus by using both cytogenetic and molecular techniques. Three distinct clinical pictures, resulting from 1q21-25, 1q 25, 32 and 1q42-qter monosomies, respectively, were recognised (7). Patients with 1q 25.3-32.1 chromosome deletion, which overlaps the deletion observed in our patient, had a severe phenotype, including pre- and postnatal growth deficiency, psychomotor retardation, and facial dysmorphism, such as microphthalmia, short and bulbous nose, cleft lip and palate, oligodontia, poorly modelled auricles and small hands and feet with short fingers and toes. Severe congenital heart defect have also been described (8, 9).

Our case showed clinical features and neurodegenerative defects similar to Dandy-Walker's syndrome and bilateral clubfoot although markedly milder, therefore not comparable to others more severe phenotypes. The mild phenotype observed in our patient could be explained as being the result of a smaller deletion.

Conclusions

At last 30 genes are localized in our region but anyone is responsible for mental retardation, moreover there is not a parallelism between clinical features and 1q interstitial deletions, so that patients carrying deletions of different extent show similar phenotypes (2).

Sonographic evidences of morphological fetal malformations assemble to Dandy-Walker's syndrome suggest, in case of late US assessment, to flank together classic cytogenetic analysis molecular cytogenetic Array-CGH technique. Array-CGH has the potential to deliver a higher resolution test compared with G- banded

chromosome analysis, allowing detection and characterization of submicroscopic copy number variants.

Array-CGH also permits a rapid response, so that it becomes significant when there is a genotype-phenotype correlation. This technique represents an improved diagnostic tool for prenatal detection of chromosomal abnormalities, allowing identification of submicroscopic clinically significant imbalances that are not detectable by conventional karyotyping, even if a genetic consult is always suggestible for a complete prenatal diagnosis (10).

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