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13q31.1 microdeletion: A prenatal case report with macrocephaly and macroglossia

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ABSTRACT

We report on a female fetus with macrocephaly and macroglossia harbouring 13q31.1 microdeletion encompassing three genes: *SPRY2*, *NDFIP2* and *RBM26*. NDFIP2 protein is involved in ubiquitination and in Ras/mitogen-activated protein kinase (MAPK) signaling pathways. SPRY2 protein is part of Sprout protein family and inhibits the Ras/MAPK pathways. Ras/MAPK pathway plays important role in complex cellular programs including cell differentiation and proliferation. Germline mutations in genes encoding protein involved in the MAPK cascade is responsible for a wide family of developmental disorders known as RASopathies. Some RASopathies, such as Costello syndrome, present a phenotype with (relative) macrocephaly as perinatal features. However, prenatal-onset macroglossia are generally absent in this syndrome but rather suggestive of the Beckwith–Wiedemann syndrome for which molecular testing were negative. Phenotype-genotype correlation with patients from DECIPHER defines *NDFIP2* and *SPRY2* as a possible candidate genes for a RASopathy potentially responsible for the clinical features in the fetus. Finally, this original case of 13q31.1 microdeletion underlines the importance of array-CGH in prenatal diagnosis with sonographic signs such as macroglossia and/or macrocephaly. In this case, genetic investigation should be not limited to the search of well-known genetic causes and other genomic microdeletions should be considered as alternative diagnoses for macroglossia.

1. Introduction

The Beckwith–Wiedemann syndrome (BWS; MIM#130650) is the most identified cause of macroglossia (Prada et al., 2012). BWS is a multiple congenital anomalies syndrome associated to molecular defects of the imprinting control region on chromosome 11p15.5 (Weksberg et al., 2005). It is characterized by clinical major findings such as abdominal wall defect, macroglossia, macrosomia, hemihyperplasia, earlobe defects, visceromegaly of intra-abdominal organs, embryonal tumor in childhood, renal abnormalities, positive family history, cleft palate and adrenal cytomegaly (Weksberg et al., 2010). Prenatal-onset macroglossia should be considered as a strong prenatal finding suggestive of the BWS and could justified first prenatal genetic investigation of the BWS (Weksberg et al., 2010). Other rarer etiologies have been also involved in isolated or syndromic macroglossia (Prada et al., 2012). Few microdeletions in 9q34, 18q23 or 12q21.31 have been associated with a large protruding tongue in patients (Yatsenko et al., 2005; Lirussi et al., 2007; Baple et al., 2010) as well as some

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RASopathies, a family of pathologies linked to abnormalities of *Ras/mitogen activated protein kinase (MAPK)* signaling pathway (Prada et al., 2012). Interestingly, some RASopathies such as Costello syndrome include macrocephaly as a key prenatal sign (Lin et al., 2009; Myers et al., 2014), a feature found in our presented case. Many genes and proteins are involved in the regulation of this pathway. In this article, we present a new *de novo* 3.34 Mb microdeletion identified by array-CGH in a female fetus with macroglossia and macrocephaly appeared in the third trimester of pregnancy. This deletion encompasses three genes *RBM26*, *NDFIP2* and *SPRY2*, two of which (*NDFIP2* and *SPRY2*) are involved in the Ras/MAPK pathway (Yusoff et al., 2002; Mund and Pelham, 2010) and may be responsible for the phenotype. This original case underlines the importance of array-CGH in the prenatal investigation of sonographic signs like macroglossia and macrocephaly and could help identified rare chromosomal imbalances and new etiologies for macroglossia.

2. Method and material

2.1. Clinical description

Our case is a female fetus of non-consanguineous parents originated from North Africa (Maghreb, Morocco). Her mother gravida 2, para 1, was 27 years old at time of conception. She had a major depression episode and suicide attempt as personal history and active smoking reduced at the beginning of her second pregnancy. The father was 29 years old at time of conception and has no significant personal history. Their first 2-year-old girl is healthy.

First trimester ultrasound of this pregnancy at 12 gestational weeks (GW) showed a nuchal translucency at 2.6 mm for a crown-rump length at 68 mm. Combined first trimester screening test of trisomy 21 showed a risk of 1/2276 (threshold risk: 1/250). Second trimester ultrasound examination displayed a harmonious growth: biparietal diameter (BPD), 5.5 cm (0DS), occipital frontal circumference (OFC) 20 cm (0DS), abdominal circumference (AC) 17.6 cm (0DS) and femur length (FL) 3.7 cm (0DS).

The third trimester ultrasound examination revealed macroglossia (Fig. 1) and overgrowth of the cephalic pole with BPD 8.7 cm (>3DS), and OFC 31.3 cm (>3DS). Magnetic Resonance Imaging confirmed no other abnormality associated and confirmed macrocephaly.

Fetal karyotype revealed normal female karyotype 46,XX. The research for abnormalities of the imprinted genes in 11p15.5 was negative.

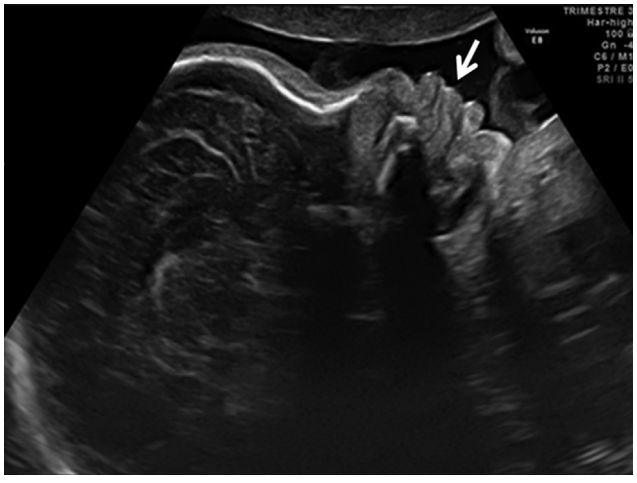

Fig. 1. Morphologic ultrasounds at 32 GW (gestational weeks): sagittal lane showing macroglossia (white arrow).

Foetopathological examination revealed craniofacial dysmorphic features including flattened face, everted nostrils, broad nasal base, short nose and enlarged mouth with a major macroglossia (length 6 cm; weight 7 g, >3DS). No ear abnormalities were observed. Histology remained without particularities, especially without adrenal cytomegaly.

2.2. Chromosomal microarray analysis (CMA)

Array-CGH was performed using a 180,000-oligonucleotide microarray (Human Genome CGH Microarray Kit 180K, Agilent Technologies, Santa Clara, CA) and following the manufacturer's instructions. The average spacing of the probes is 13 kb. DNA from the patient was compared with DNA from two other patients with different diseases, according to the loop model. Genomic Workbench software, standard edition 6.5 (Agilent) was used to interpret the results with the following parameters: aberration algorithm ADM-2, threshold 6.0, fuzzy zero, centralization, and moving average window 0.5 Mb. A copy number variation (CNV) was noted if at least three contiguous oligonucleotides showed an abnormal log2 ratio (>+0.58 or <−1 according to the Alexa 5 deviation) with a mirror image. The Database of Genomic Variants (DGV, http://projects.tcag.ca/variation/) was used to compare findings to previously reported studies. Coordinates of all variations or probes are based on the UCSC GRCh37/hg19 assembly.

2.3. Fluorescence in situ hybridization

To confirm array-CGH results, fluorescent in situ hybridization analysis (FISH) on the fetus and parents were performed on metaphase chromosomes derived from cultured amniocytes and peripheral blood lymphocytes respectively using a 13q31.1 specific probe localized within the 3.34 Mb deletion (RP11-695N3).

3. Results

Array-CGH revealed a large heterozygous deletion of 3.34 Mb in the 13q31.1 region (Fig. 2) encompassing three genes: *RBM26*, *NDFIP2* and *SPRY2*. The 3.34 Mb deletion extends from base pair 79,618,555 (first deleted oligonucleotide) to 82,959,164 (last deleted oligonucleotide) (GRCh37/hg19) from the 13p telomere. No other abnormalities larger than three probes were observed, excluding well-known benign copy number variant. FISH analysis on the fetus confirmed the 13q31.1 heterozygous deletion. FISH on the peripheral blood lymphocytes obtained from both parents showed two signals suggesting that the abnormality detected in the fetus occurred *de novo*. Our case molecular details have been referenced in DECIPHER database (Firth et al., 2009) for chromosomal aberrations: # 278458.

4. Discussion

In this report, we describe a 3.34 Mb *de novo* 13q31.1 microdeletion in a female fetus presenting with macrocephaly and macroglossia. This large deletion encompasses only 3 known protein-coding genes: *RBM26* (RNA binding motif protein 26), *NDFIP2* (Nedd4 family interacting protein 2) and *SPRY2* (Sprouty homolog 2) (Fig. 2). No known function has yet been ascribed to *RBM26*. NDFIP2 protein is involved in the ubiquitination process, by activating Nedd4 family of E3 ubiquitin ligases. NDFIP2 is also involved in regulation of Ras/MAPK signaling pathways (Mund and Pelham, 2010). SPRY2 protein is part of Sprouty family proteins and is known to be an inhibitor of the Ras/MAPK pathway (Yusoff et al.,