European Journal of Medical Genetics 59 (2016) 48–51

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Clinical report

Prenatal diagnosis of Nager syndrome in a 12-week-old fetus with a whole gene deletion of *SF3B4* by chromosomal microarray

Ida Charlotte Bay Lund [a, *], Else Marie Vestergaard [a], Rikke Christensen [a], Niels Uldbjerg [b], Naja Becher [a]

[a] Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

Article history:
Received 6 July 2015
Received in revised form
24 October 2015
Accepted 1 December 2015
Available online 9 December 2015

Keywords:
Nager syndrome
Acrofacial dysostosis
Chromosomal microarray
Prenatal diagnosis
SF3B4

ABSTRACT

Less than one hundred cases of the acrofacial dysostosis, Nager syndrome, have been described. The cardinal features of Nager syndrome are micrognathia, midface retrusion and limb malformations, predominately of the radial ray of upper extremities. Within the past three years haploinsufficiency of *SF3B4* has been confirmed as the major cause of Nager syndrome. Different loss-of-function point-mutations in *SF3B4* have been found in approximately 2/3 of patients diagnosed with Nager syndrome. Whole gene deletions of *SF3B4* have also been suggested to be the cause of Nager syndrome in *SF3B4* point mutation negative patients. Only four prenatal cases displaying Nager-like features in the 2nd or 3rd trimester which have been genetically confirmed with *SF3B4* point-mutation after birth have been described. We report a case of a 12-week-old fetus with micrognathia, malformed wrists, bilateral club foot and short long bones diagnosed prenatally by chromosomal microarray with a *de novo* 0.4 Mb deletion at chromosome 1q21.2 involving *SF3B4*. To our knowledge, this is the first report of Nager syndrome caused by a *SF3B4* whole gene deletion. The case presented also shows that high-resolution chromosomal microarray in early pregnancy can confirm Nager syndrome caused by SF3B4-deletion prenatally.

1. Introduction

Nager syndrome (NS) belongs to the group of disorders named acrofacial dysostoses (AFDs) and was first described in 1948 by Nager and de Reyenier(Bernier et al., 2012). Less than one hundred cases have been reported of which eight were prenatal cases detected in the 2nd or 3rd trimester (Benson et al., 1988; Gana et al., 2013; Couyoumjian et al., 2008; Castori et al., 2014; McPherseon et al., 2014; Petit et al., 2014; Ansart-Franquet et al., 2009; Waggoner et al., 1999). The first reported case of prenatal NS detected by ultrasonography dates back to 1988 describing a fetus in 30th week of gestation with hypoplastic mandible, malrotated external ears and truncated upper limbs(Benson et al., 1988). Other cardinal features of NS include micrognathia, midface retrusion, hypoplasia of the malar eminences and zygomata, downslanting palpebral fissures and preaxial upper limb defects(Bernier et al., 2012). Micrognathia may lead to tracheostomy in early childhood and approximately 20% of reported NS cases die neonatally (Bernier et al., 2012; McPherson et al., 2014). Mental development is usually normal or mildly delayed(Czeschik et al., 2013).

In 2012, Bernier et al.(Bernier et al., 2012) discovered that heterozygosity for a mutation in the SF3B4-gene (1q21.2) caused NS in approximately 2/3 of the patients; these findings were confirmed by Petit et al.(Petit et al., 2014) and Cszeschik et al.(Czeschik et al., 2013) in 2013. *SF3B4* encodes a spliceosome-associated protein (SAP49), a component of a spliceosomal complex presumably responsible for the splicing of genes involved in limb and craniofacial development. Furthermore, SAP49 is also linked to bone morphogenic proteins in chondrogenesis of the embryonic skeleton (Czeschik et al., 2013).

Until now, 32 distinct *SF3B4* mutations have been reported in 38 unrelated patients (Bernier et al., 2012; Petit et al., 2014; Czeschik et al., 2013), including four cases diagnosed prenatally by ultrasonography and subsequently genetically confirmed after birth or at termination of pregnancy (Castori et al., 2014; McPherson et al., 2014; Petit et al., 2014; Ansart-Franquet et al., 2009). All reported

* Corresponding author. Department of Clinical Genetics, Aarhus University Hospital, Brendstrupgaardsvej 21C, DK-8200 Aarhus N, Denmark.
E-mail address: idacharlottebaylund@dadlnet.dk (I.C.B. Lund).

http://dx.doi.org/10.1016/j.ejmg.2015.12.001
1769-7212/

mutations are predicted to cause loss of function of *SF3B4*. Therefore, wholegene deletions of *SF3B4* have also been suggested as a possible cause of NS in point mutation negative patients(Bernier et al., 2012).

We present the first reported case of NS diagnosed prenatally in gestational week 12 by high-resolution chromosomal microarray (CMA) involving a whole gene deletion of *SF3B4*.

2. Clinical report

A 37-year-old Caucasian woman (para 0, gravida 1) undergoing first trimester routine ultrasonography screening at 11 + 5 weeks of gestation. The examination revealed a fetus with micrognathia (Fig. 1), malformed wrists and a large head circumference relative to abdominal circumference. The head circumference was normal to crown rump length. Based on crown rump length due date was moved forward six days compared to last period. Increased nuchal translucency measurement at 3.6 mm. The woman was healthy with a Body Mass Index of 27.7 kg/m^2. She had not been exposed to teratogenic agents prior to the spontaneously conceived pregnancy with a non-consanguineous partner.

Based on the ultrasonography findings the pregnant couple consented to chorionic villus sampling (CVS). Rapid test (quantitative fluorescence polymerase chain reaction, QF-PCR) on DNA from the CVS for the common trisomies 21, 18, and 13, and sex chromosome aneuploidies was normal. A repeated ultrasound scan at gestational age 12 + 6 weeks revealed bilateral club foot (Fig. 2) and short long bones (z-scores, tibea −2.2, fibula −2.4, humerus −2.4, radius −3.2, ulna −4.1). The number of fingers and toes appeared normal. On parental request the pregnancy was terminated before further results from genetic analyses were available. Fetal autopsy was not performed.

A standard chromosome analysis (cultured CVS) confirmed a normal karyotype (46,XY). Subsequently, CMA (array Comparative Genomic Hybridization (CGH), Agilent, 180 K) was performed on DNA extracted from cultured chorionic villus cells. This analysis showed a *de novo* 0.4 Mb deletion at chromosome 1q21.2 (arr[hg19] 1q21.2(149852674–150257430)x1dn) involving 15 refseq genes including *SF3B4* (Fig. 3). CMA was carried out on both parents with normal results. The deletion has been submitted to a public database (Decipher, 318412) with the parents' consent.

3. Discussion

To our knowledge this case is the first to report a whole gene

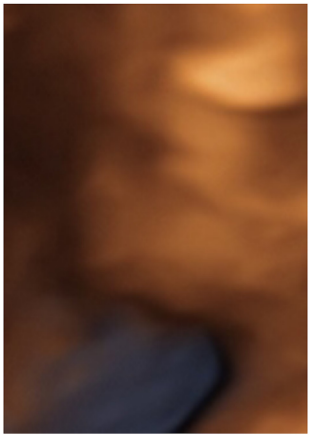

Fig. 1. Prenatal ultrasound scan at 11 + 5 weeks of gestation showing micrognathia.

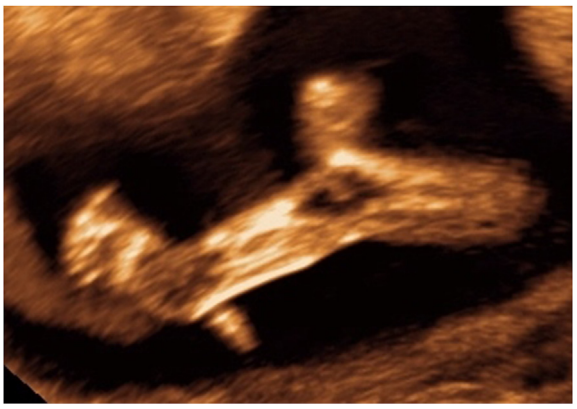

Fig. 2. Prenatal ultrasound scan at 12 + 6 weeks of gestation showing club foot.

SF3B4 deletion detected by CMA in a fetus with an NS phenotype. With the discovery of *SF3B4* loss of function mutations as the cause of NS, Bernier et al.(Bernier et al., 2012) also suggested that whole gene deletions of *SF3B4* could be responsible for NS in *SF3B4* point mutation negative patients. Recent studies have examined NS patients that are *SF3B4* point mutation negative with CMA showing normal results. However the platforms used in these studies had low coverage in the region of *SF3B4* (Petit et al., 2014; Czeschik et al., 2013). In the prenatal cases of Ansart-Franquet(Ansart-Franquet et al., 2009) and McPherson(McPherson et al., 2014) (Table 1) CMA analyses also showed normal results; in the former case, platform characteristics were unavailable for comparison and in the latter case a prenatal 135 K oligonucleotide microarray was applied. We have used the non-targeted high resolution CMA, 180K array CGH platform from Agilent, which has previously demonstrated a high detection rate of fetal subchromosomal abnormalities (Vestergaard et al.,2013; Lund et al., 2015).

In addition to *SF3B4*, only one other gene, *VPS45A*, in the deleted region has been described with clinical involvement. Homozygosity or compound heterozygosity for a mutation in the *VPS45A* gene is associated with neutropenia(Vilboux et al., 2013). The other genes in the deleted region have not previously been reported in relation to disease. We believe that lack of *SF3B4* primarily explains the phenotype of the fetus, but we cannot rule out that deletion of the other genes in the region may have affected the fetal phenotype. The lethal NS case described by Waggoner et al.(Waggoner et al., 1999) (Table 1) diagnosed by standard chromosome analysis most likely included the *SF3B4* gene but also several other genes that might have influenced the phenotype.

Table 1 compares the present prenatal case with recent publications (Castori et al., 2014; McPherson et al., 2014; Petit et al., 2014; Ansart-Franquet et al., 2009; Waggoner et al., 1999). Only prenatal cases with a genetically confirmed NS diagnosis are included because a distinct categorization of NS from the other AFDs, based solely on prenatal ultrasound, is difficult to achieve (Online Mendelian Inheritance in Man). E.g. McPherson et al.(McPherson et al., 2014) (Table 1) discussed whether their case represents Rodrigiuez syndrome (RS), another AFD, or a severe form of NS. RS includes micrognathia, resembling NS, but the limb involvement is more severe than in NS with both pre- and/or post-axial upper and lower limb defects. The case of McPherson et al. (McPherson et al., 2014) was diagnosed clinically as RS after birth but whole-genome sequencing revealed a disease-causing *SF3B4* point mutation. The genetic cause of RS has not yet been established and McPherson et al. suggest that NS and RS might be allelic disorders. This is supported by our present findings of both pre- and post axial truncated upper limbs and lower limb defects resembling