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Restrictive dermopathy: Novel *ZMPSTE24* mutation and clues for prenatal diagnosis

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Abstract

Background: Prenatal diagnosis of Restrictive Dermopathy (RD) in routine ultrasonography is particularly challenging since most fetal ultrasonography RD findings are non-specific and appear during late pregnancy.

Main observations: Here we describe a case report of a couple of apparently non consanguineous parents that requested a genetic counseling after two consecutive complicated pregnancies that ended with the premature delivery of two male infants with multiple congenital anomalies; the first was a stillborn, while the second died at 8 days old. Clinical Exome Sequencing (CES) identified a homozygous variant in the ZMPSTE24 gene of the newborn, which in turn was heterozygous in the parents, confirming the diagnosis of RD.

Conclusions: Comparison of prenatal data of present patients with those from the literature indicates that some fetal movements, microretrognathia, join contractures, and polyhydramnios are recurrent in RD and their recognizable combination, together with application of CES, could help the prenatal and/or postnatal diagnosis of this rare condition.

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Introduction

Restrictive dermopathy (RD, MIM# 275210) is a rare neonatal lethal condition, with a prevalence <1/1,000,000 newborns [1]. Neonatal features are represented by thin and tight skin, typical facial dysmorphism (sparse eyelashes and eyebrows, small mouth fixed in the "O" position, micrognathia, dysplastic ears), and arthrogryposis multiplex. Bone mineralization defects and dysplastic clavicles are also frequent. Most affected newborns die in the first week due to respiratory insufficiency [2].

Most cases are caused by autosomal recessive mutations in the Zinc Metallopeptidase STE24 gene (*ZMPSTE24*); less frequently by *de novo* dominant mutations in the Lamin A/C gene (*LMNA*) [3]. Pregnancies with fetal RD shows intrauterine demise, polyhydramnios, prematurity, premature rupture of membranes, and fetal akinesia deformation sequence (decreased fetal movements, intrauterine growth restriction (IUGR), arthrogryposis and pulmonary hypoplasia) [4]. Prenatal diagnosis is very challenging without a genetic test, due to non-specific late ultrasonography findings, often appearing only in the third trimester [4].

Case Report

Here we describe a case report of a couple of apparently healthy, non-consanguineous parents from Caucasian origin that requested a genetic counselling after two consecutive complicated pregnancies that ended with the premature delivery of two male infants with multiple congenital anomalies; the first was a stillborn, while the second died at 8 days old (Figure 1A). Molecular analyses were performed in the second child, from whom biological material was available, and both parents.

Patient 1

The first pregnancy presented normal ultrasonography in the first trimester. At 21+0 week gestational age (wGA) appropriate fetal growth was observed, but several fetal anomalies were suspected: low set ears, retromicrognathia, pinched nose, mouth often fixed in an open position, upper lip with downslanting corners, thick philtrum, hyperechogenic bowel, ascites, and tendency to fixed positions of some joints (Figures 1B and 1C). Maternal perception of reduced fetal movements and repeated episodes of vaginal leaks (suspected preterm premature rupture of membranes [PPROM]) were referred starting from ≈24 wGA. Oligohydramnios, hydrothorax with mediastinal shift, hyperechogenic small lungs and bowel, bilateral hydrocele testis, intrauterine growth restriction (IUGR), and abnormal cardiotocography (CTG) were observed. A male stillborn was delivered by cesarean section at 31 wGA. Major anomalies included very tight skin with several lacerations, diffuse rigidity with proximal and distal arthrogryposis, very small nose, protruding eyes, and micrognathia. Autopsy was limited by maceration. A karyotype was performed from skin and showed a normal male 46, XY karyotype.

Patient 2

The second pregnancy presented normal ultrasonography in the first trimester. At 21+4 wGA fetal growth was appropriate; left ventricular hyperechogenic focus, dilated left renal pelvis and poorly filled stomach were observed; micrognathia was observed. PPROM was suspected at 22 wGA. At 24 wGA, amniotic fluid index was at the 20th percentile. Amniocentesis for fetal karyotyping was performed at 24+5 wGA and proved to be normal [46,XY]. FISH test for 22q11.2 deletion was negative. At 28 wGA PPROM, abnormal CTG, and IUGR leaded to cesarean section. The newborn was intubated; APGAR score was 4 at 1 minute and 5 at 5 and 10 minutes. The baby presented with progeroid appearance with tight translucent skin with underlying blood vessels clearly visible, severe microretrognathia, small nose, long philtrum, small "O"-shaped mouth, low set and small ears, stiff joints with severe restriction of movements, choanal stenosis, atrial septal defect, mild hepatomegaly, and dilated renal pelvis (Figures 1D and 1E). The baby died at 8 days old due to cardiocirculatory arrest and impossibility of intubation because of severe micrognathia and neck rigidity.

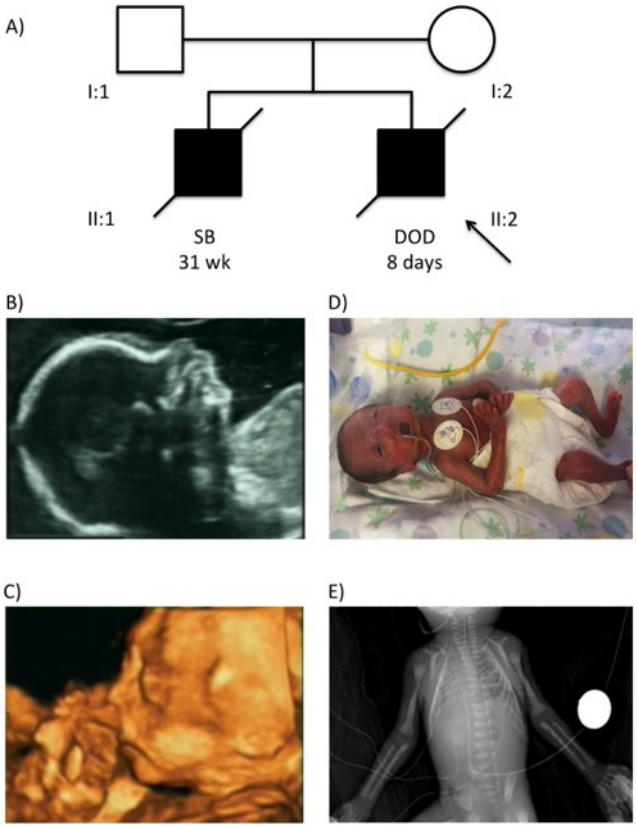

Figure 1: Clinical and genetic data of reported family. (A) Family pedigree. Squares and circles indicate male and female family members, respectively. Arrow indicates proband. Solid symbols are affected individuals. DOD, date of death; SB, stillbirth; wk, week. (B) Ultrasound ecography of the first fetus presenting with microretrognathia. (C) Ultrasound ecography of the first fetus presenting with low set ears and dysmorphic mouth with down turned upper lip at the 21st week of gestation; (D) Picture of the second child, presenting with the typical RD facial dysmorphisms, thin and translucent skin, and arthrogryposis. (E) Total body Rx revealing hypoplasia of the distal third of clavicles, a defect of ossification at C2, and abnormal positioning of the scapula.

Molecular findings

A blood sample was obtained from patient 2 and both parents; cytogenomic microarray was normal (data not shown). A clinical exome sequencing (CES) analysis was then requested for the trio. A TruSightOne sequencing panel kit (Illumina, San Diego, CA, USA) was used to analyze 4813 genes associated to human genetic diseases. The enriched libraries were sequenced by a NextSeq500 instrument (Illumina). CES data were processed and analyzed using an in-house implemented pipeline as previously described [5]. Among a total of 8,000 variants we identified 10 variants compatible with autosomal recessive mode of inheritance. We considered as the best candidate a homozygous variant in the *ZMPSTE24* gene (NM_005857.4: c.954+1G>A; rs781706477) (Supplementary Figure 1A) located

in a canonical splicing site with a minor allele frequency (MAF) of 0.0012% in the gnomAD public database of genetic variants (http://gnomad.broadinstitute.org/). This variant, confirmed by Sanger sequencing, was present in heterozygous state in both parents (Supplementary Figure 1B), and was deemed to completely abolish splicing function by *in silico* prediction tools (Supplementary Figure 1C).

Discussion

The majority of RD patients are homozygous or compound heterozygous for null mutations in the *ZMPSTE24* gene [3] resulting in lack of protein activity, consequent accumulation of prelamin-A isoforms and absence of mature lamin A. This leads to a fatal clinical course of the disease and a prenatal or neonatal death [3]. Generally, the severity of phenotype varies according to the type of *ZMPSTE24* mutations and to the degree of enzyme activity reduction. The c.954+1G>A mutation is a plausible deleterious loss-of-function (null) mutation, as expected by the phenotype of the two male infants compatible with classical RD clinical features [3].

In routine ultrasonography, prenatal diagnosis of RD is a challenge since most fetal ultrasonography RD findings are non-specific and appear only late in the second/third trimester. Ultrasound examinations in the two pregnancies reported here revealed that some fetal anomalies associated with RD could be recognized at ultrasound scans already in the second trimester. In particular, a comparison of prenatal data of the present patients with those from a review of the literature [6-8] strongly suggest that some fetal abnormalities, such as microretrognathia, small/pinched nose, reduction of fetal movements, and intrauterine join contractures are recurrent in RD and their recognizable combination could help the prenatal and/or postnatal diagnosis of this rare condition (Table 1).

Tables

Table 1: Comparison of selected clinical features from pregnancies complicated by RD of the fetus

	Present report		Mulder et al., 2001 [6]			Van der Stege et al., 1997 [7]	Feldman-Leinder et al., 2008 [8]
	Patient 1	Patient 2	Case 1	Case 2	Case 3		
Facial dysmorphisms at fetal ultrasonography	+	+	+	+	+	+	+
Retromicrognathia	+	+	+	+	-	-	+
Small/pinched nose	+	-	+	+	+	-	+
Persistent open mouth / microstomia	+	-	+	-	-	+	+
Reduced fetal movements/fixed joints	+	+	-	+	-	+	+
IUGR (III trimester)	+	+	+	+	+	+	-
PPROM	+	+	Possible	Possible	Possible	+	NA

IUGR, intrauterine growth restriction; NA, not available; PPROM, premature rupture of membranes

Conclusions

In conclusion, we have successfully used NGS to diagnose RD in two male infants with multiple congenital anomalies and identified a novel homozygous *ZMPSTE24* mutation. Present data expand the mutation spectrum of *ZMPSTE24* gene and provide further support to the use of CES in the early diagnosis of fetuses with multiple congenital anomalies. Moreover, they provide clear evidence that some specific RD-associated prenatal sonographic findings can be recognized from the second trimester and can be used to drive molecular diagnosis.

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