Title: Achondrogenesis 1A- a rare lethal type of skeletal dysplasia (ePBGC04)

Authors: Praisy Joy, Neelu Sontakke, Jasmina Begum, Usha Devi, Tapas Som.

Affiliation: Perinatal Clinic , AIIMS Bhubaneswar, Odisha, India-751019.

Introduction

The skeletal dysplasias are a heritable group of more than 450 well delineated disorders that affect primarily bone and cartilage, but can also have significant effects on muscle, tendons and ligaments. Here we present a case of achondrogenesis type 1A.

Achondrogenesis type 1A is a rare type of skeletal dysplasia with an incidence of 1 in 40,000 live births, caused due to mutation in the TRIP11 gene [1-3]. The varied presentation of this disorder has been described in the literature, including short thorax, defective formation of long bone, skull and vertebral anomalies[4-6]. In this case, the ultrasound diagnosis of skeletal dysplasia was made by the anomaly scan showing a narrow thorax, cloverleaf skull, short long bones and sacral agenesis.

Achondrogenesis type I is a severe chondrodystrophy.

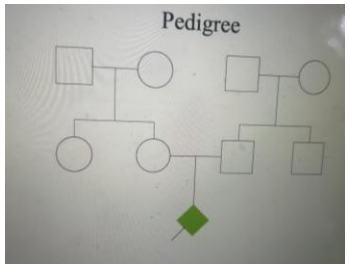
It is classified into Achondrogenesis I and Achondrogenesis II.

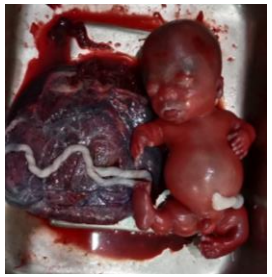
Further Achondrogenesis 1 is divided into IA and IB (1-4).

The thyroid hormone receptor interactor 11 (TRIP11), also known as Golgi-associated microtubule-binding protein 210 (GMAP-210) plays essential roles during skeletal differentiation and development.

Clinical history:

A 35 year female, a primi, non-consanguineously married presented to the perinatal clinic. Her 1st pregnancy scans showed multiple congenital anomalies and was terminated at 19 weeks of gestation. The anomaly scan showed sacral agenesis, narrow thorax, vertebral flattering, small bones of upper and lower limbs, hypoplastic forelimbs and hindlimbs with very short femur, tibia, fibula, humerus and distorted alignment of spine, the features being suggestive of skeletal dysplasia, thanatophoric dysplasia or asphyxiating thoracic dystrophy. She has been evaluated for carrier status of pathogenic variations.

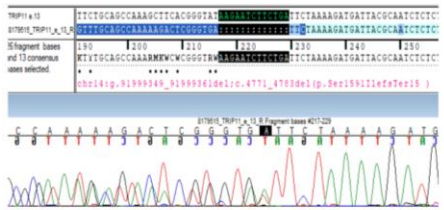




Results/Observations

Whole exome sequencing revealed a heterozygous variant in TRIP11 gene. Genetic testing revealed both partners carrying heterozygous mutation in TRIP11 gene (c.4771_4783del ; p.Ser1591IlefsTer15).

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
TRIP11 **(-)** (ENST00000267622.8)	Exon 13	c.4771_4783del **(p.Ser1591IlefsTer15)**	Heterozygous	Achondrogenesis, type IA (OMIM#200600) / Odontochondrodysplasia 1 (OMIM#184260)	Autosomal recessive	Likely Pathogenic **(PVS1, PM2)**



Discussion:

Golgins are a family of coiled-coil proteins associated with the Golgi apparatus necessary for tethering events in membrane fusion and as structural supports for Golgi cisternae. GMAP-210 belongs to the Golgin protein family and localizes to the cis-Golgi network. It is involved in microtubule binding and serves as a tethering factor required for endoplasmic reticulum (ER) to Golgi vesicle transport in the early secretory pathway . It plays essential roles in Golgi organization and structure maintenance.

Genetic Counselling:

The twenty-five percent risk of TRIP11 and the need for prenatal diagnosis in the subsequent pregnancy was explained to the couple. Various options like Prenatal diagnosis, preimplantation diagnosis and adoption were also discussed with the couple.

References

1.Bokesoy, I., Aydin, E., Gazilerli, S. **A case of achondrogenesis type I.** Hum. Genet. 67: 349-350, 1984.

2.Borochowitz, Z., Lachman, R., Adomian, G. E., Spear, G., Jones, K., Rimoin, D. L. **Achondrogenesis type I: delineation of further heterogeneity and identification of two distinct subgroups.** J. Pediat. 112: 23-31, 1988.

3.Fraccaro, M. **Contributo allo studio delle malattie del mesenchima osteopoietico: l'acondrogenesi.** Folia Hered. Path. 1: 190-208, 1952.

4.Golbus, M. S., Hall, B. D., Filly, R. A., Poskanzer, L. B. **Prenatal diagnosis of achondrogenesis.** J. Pediat. 91: 464-466, 1977.

5.Smith, W. L., Breitweiser, T. D., Dinno, N. **In utero diagnosis of achondrogenesis, type I.** Clin. Genet. 19: 51-54, 1981.

6.Smits, P., Bolton, A. D., Funari, V.,et al.,. **Lethal skeletal dysplasia in mice and humans lacking the golgin GMAP-210.** New Eng. J. Med. 362: 206-216, 2010.