

Negative exome in a fetus affected by Agnathia-otocephaly complex

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Introduction

Agnathia-otocephaly is rare condition with a frequency of 1 in 70,000 births. It is characterized by mandibular hypoplasia, ear malposition, brain malformations and considered lethal. The embryological origin is a defect affecting the blastogenesis of the first branchial arch derivatives. *PRRX1* was reported in 2011 as the etiology of agnathia-otocephaly complex; interestingly with monoallelic and biallelic mutations. Other gene also associated is *OTX2*, that is related with syndromic microphthalmia type 5 with autosomal dominant inheritance.

Clinical case

Fetus was diagnosed at 18 weeks with increased cranial diameters due to severe bilateral symmetrical ventriculomegaly, absence of cavum of the septum pellucidum, agenesis of the corpus callosum, agnathia, nasal bone present, low set of ears, dextrocardia, atrioventricular canal defect and an abnormal outflow tract characterized by one vessel, most probably a common arterial trunk.

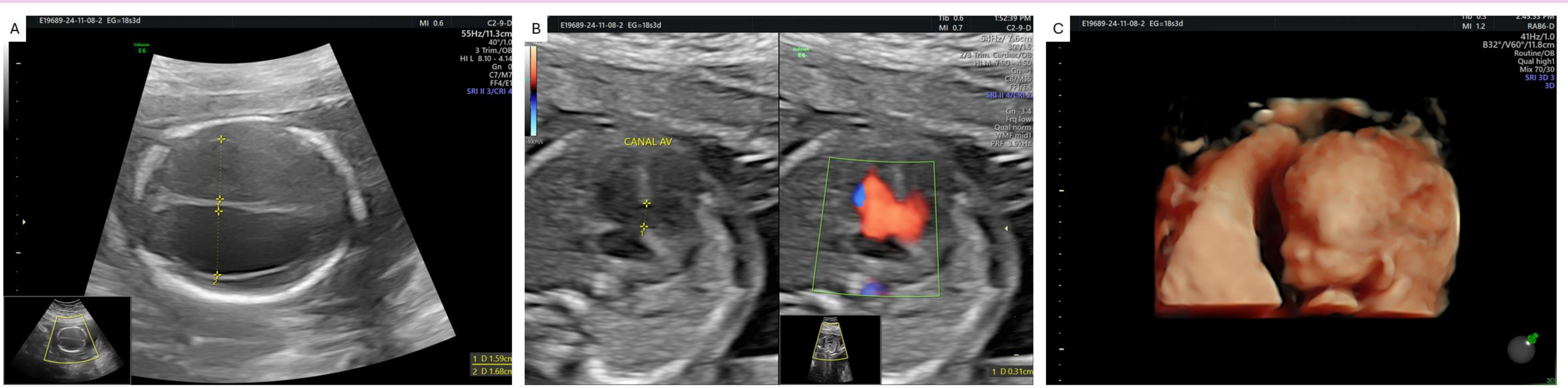


Figure 1. A. Severe bilateral symmetrical ventriculomegaly. B. Four chamber view showing atrioventricular canal defect. C. 3D profile of the face showing mandibular aplasia and otocephaly.

Results

After consultation with a multidisciplinary team, patient decided to proceed with a termination of pregnancy and genetic testing after delivery. The fetus was evaluated by clinical geneticist after delivery and *situs inversus* was confirmed by dissection.

DNA was extracted from skin. Exome sequencing with CNV analysis was performed in a CLIA/CAP certified lab. No relevant variants were found in *PRRX1* or *OTX2* genes, only a novel heterozygous *TRIM71* p.Asp654His variant was highlighted by bioinformatic analysis. *TRIM71* causes congenital hydrocephalus type 4 (OMIM 618667) and this disorder does not fit on the fetal phenotype.

Conclusions

In this fetus it was possible to establish the diagnosis of agnathia-otocephaly complex by prenatal ultrasound. No causative variants were found by exome and chromosomal microarray in fetal skin supporting a non-common mutation mechanism, genetic heterogeneity or a phenocopy of the syndrome in this patient of Latino ancestry.

Optima Cytoscan chromosomal microarray (Figure 2) was also normal.



Figure 2. A. Fetus with agnathia-otocephaly. B. Microarray with result arr (X,Y)x1,(1-22)x2 with log2 global view showing no CNV at a whole chromosomal or deletion or duplication at 1q or 14q.