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EXPANDING THE PRENATAL AND POSTNATAL PHENOTYPE OF 1Q21.1 DUPLICATION: A CASE REPORT

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BACKGROUND

- Recurrent duplications involving chromosome 1q21.1 have been associated with high phenotypic diversity, including a normal phenotype.[1]
- These microduplications display variable expressivity and incomplete penetrance, even among family members with the same copy number variant (CNV).[1]
- Previously described prenatal features include fetal ventriculomegaly, nasal bone aplasia, cardiac anomalies, duodenal atresia, and micrognathia.[1]
- Affected individuals have a wide spectrum of features, including cardiac defects, brain anomalies, intellectual disability, developmental delay, autism, eye abnormalities, macrocephaly, facial dysmorphism, psychiatric conditions, and behavioral disturbances.[2]
- We describe a prenatally diagnosed case of 1q21.1 duplication with findings not previously reported.

CASE PRESENTATION

Presenting Illness and Medical History

- 36-year-old G6P2032 presented at 20 weeks' gestation for Maternal Fetal Medicine consultation for fetal hydrocephalus
- Past medical history, family history, social history, and medications were noncontributory
- Couple was nonconsanguineous
- Prenatal cfDNA screening was low risk for trisomies 21, 18, and 13, monosomy X, and 22q11.2 deletion syndrome and confirmed male sex
- Carrier screening for 27 autosomal recessive and X-linked conditions was negative

Diagnostic Workup

- Detailed ultrasound revealed severe bilateral ventriculomegaly, macrocephaly, an absent corpus callosum (CC), an absent cavum septum pellucidum (CSP), a dilated 3rd ventricle, and a small cerebellum with otherwise normal anatomy survey
- Fetal MRI revealed an incomplete CSP anteriorly and otherwise was consistent with ultrasound
- Fetal echocardiogram was normal
- Referred for genetic counseling and elected for amniocentesis at 21 weeks
  - FISH: Normal signal pattern for chromosomes 13, 18, 21, X and Y
  - Karyotype: 46,XY
  - Amniotic fluid AFP and PCR for cytomegalovirus, parvovirus and toxoplasmosis: Normal/negative
  - Chromosomal microarray analysis (CMA): 1.73 MB distal duplication of 1q21.1>q21.2: arr[hg19] 1q21.1q21.2(146,105,171-147,830,903) x3
    - This region includes 10 OMIM genes (*NBPF14, PRKAB2, CHD1L, FMO5, BCL9, ACP6, GJA5, GJA8, GPR89B, NBPF11*)
  - Exome sequencing: Negative except for the duplication noted on CMA

Treatment and Management

- Counseled on all management options and elected continuation of pregnancy
- Underwent neonatology and pediatric neurosurgery consultations antenatally
- Serial growth ultrasounds and antenatal testing revealed polyhydramnios at 28 weeks and large for gestational age (LGA) fetus at 31 weeks

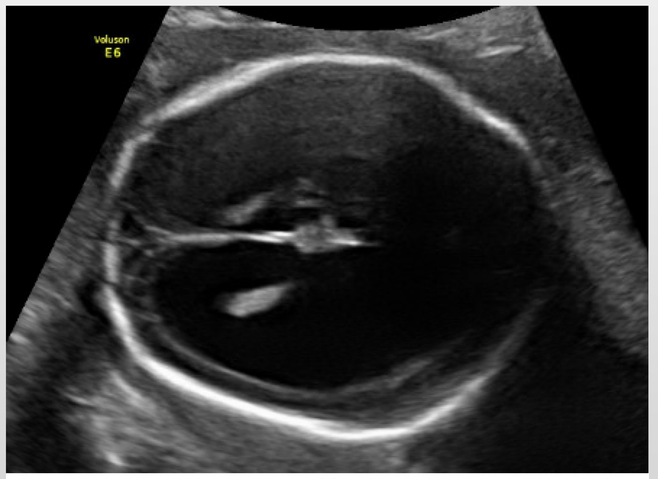

Figure 1: Transventricular view of fetal head on ultrasound at 24 weeks showing severe ventriculomegaly

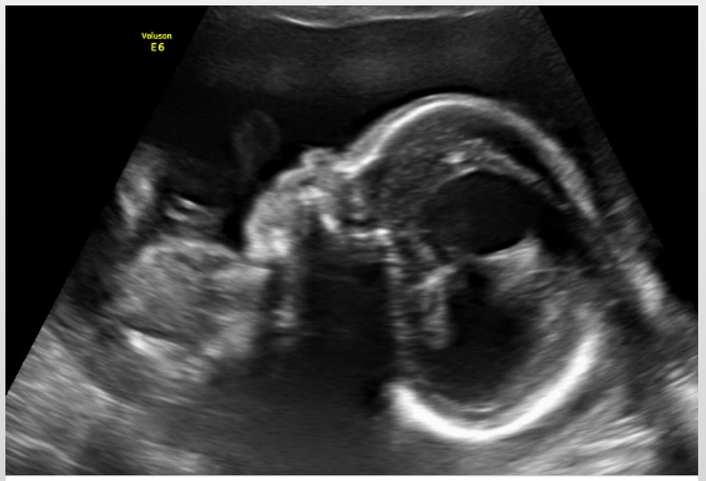

Figure 2: Midsagittal view of fetal head on ultrasound at 24 weeks showing hydrocephalus

Figure 3: Coronal view of fetal head on MRI at 22 weeks showing severe ventriculomegaly

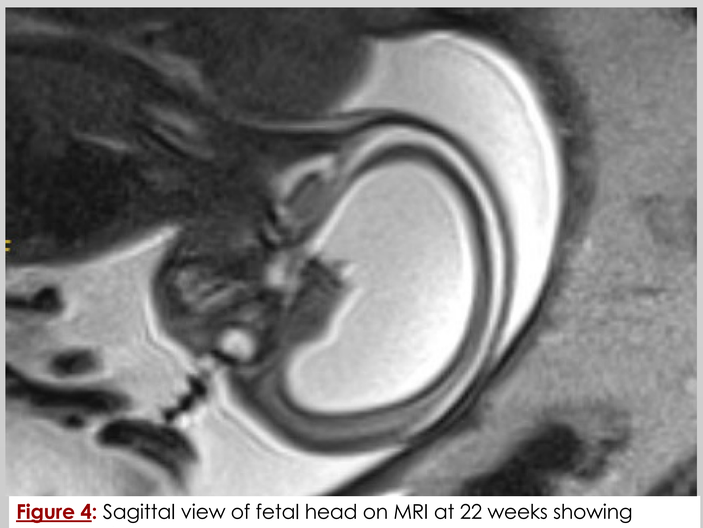

Figure 4: Sagittal view of fetal head on MRI at 22 weeks showing hydrocephalus

Outcome and Follow-Up

- Uncomplicated Cesarean delivery was performed at 36 weeks for preterm labor, decreased fetal movement, and breech presentation
- Male infant delivered with birth weight 4340 grams and APGARS 2, 6, and 7 at 1, 5, and 10 minutes
- Postnatal findings included macrocephaly with frontal bossing, a mildly dilated ascending aorta, an anorectal malformation, and disordered eye movements
- Imaging confirmed marked hydrocephalus with CC hypoplasia, absence of the CSP, and an arachnoid cyst
- Infant underwent subgaleal shunt placement and diverting colostomy on day 2 of life, third ventriculostomy at 1 week of life, ventriculoperitoneal shunt placement at 2 weeks, and anorectoplasty at 5 months
- Infant has developmental delays and is enrolled in Early Intervention

CONCLUSION

- This is the first case reporting absent CSP and an anorectal malformation in an individual with 1q21.1 duplication.
- While previous cases reported fetal ventriculomegaly, none were reported to be as severe as noted here.
- This case highlights the high phenotypic variability of 1q21.1 duplication and resulting challenges posed in genetic counseling in the prenatal setting.
- Further studies are needed to determine the function of the genes implicated in this duplication and the molecular mechanisms underlying these novel findings.

REFERENCES

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2. Bourgois A, Bizaoui V, Colson C, et al. Phenotypic and genotypic characterization of 1q21.1 copy number variants: A report of 34 new individuals and literature review. *Am J Med Genet A*. 2024;194(3):e63457.