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Expanding the fetal phenotype of *USP7*-related conditions

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Introduction

Hao-Fountain syndrome (HAFOUS) is a neurodevelopmental disorder characterized by global developmental delay, variable intellectual disability and behavioral abnormalities. HAFOUS is caused by heterozygous loss-of-function variants in *USP7*. To date, there are approximately 60 cases reported describing postnatal phenotype. Information about prenatal phenotype is significantly limited with a single case of fetal cystic hygroma reported. Other congenital anomalies described include heart defects and contractures. However, the fetal phenotype of HAFOUS largely remains unknown. We present three cases with fetal hydrops in combination with *USP7* variants including a novel splice site variant and two copy number variants.

Case presentation/diagnostic workup

	Case 1	Case 2	Case 3
Age	35	36	33
Gravity/Parity	G5P2022	G8P6016	G7P3033
Gestational age at initial presentation	12w6d	15w3d	16w6d
Specimen source	Products of conception	Placental biopsy	Amniotic fluid
Variant	734kb deletion of 16p13.2 (in addition to *USP7* deletion includes: *TMEM114*, *METTL22*, *ABAT*, *TMEM186*, *PMM2*, *CARHSP1*) arr[hg19]16P13.2(8,367,122-9,101,249)x1	*USP7* c.383_1G>Cp.? (NM_ 003470. 2)	358kb duplication of 16p13.2 (partial duplication of *USP7*) arr[hg19]16P13.2(9,018,355-9,375,856)x3
Inheritance	De novo	De novo	Unknown (parental follow-up declined)
Variant classification	Pathogenic	Pathogenic	Variant of unknown significance
Ultrasound findings	• Non-immune hydrops fetalis (cystic hygroma, pleural effusion, ascites, pericardial effusion)	• Non-immune hydrops fetalis (cystic hygroma, ascites, pleural effusion, edema) • Single umbilical artery • Oligohydramnios • Abnormal position of fetal legs	• Non-immune hydrops fetalis (skin edema, pleural effusion, ascites) • Growth restriction (EFW<1%) • Echogenic bowel • Enechoic cystic fluid within fetal buttocks • Loculated cystic structure of fetal neck, armpits, and groin • Low set ears • Short, broad nasal root with transverse skin crease
Autopsy findings	N/A (Autopsy declined)	N/A (Autopsy declined)	
Outcome	Fetal demise at 17w4d	Termination at ~16w	Fetal demise at 17w6d
Additional tests performed	• Normal parental carrier screening of *PMM2* • Normal parental qPCR for the deletion • Normal parental karyotypes	• Normal female microarray • Maternal TORCH titers (non-contributory)	• Normal proband only WES • Normal CMV/Toxo/Parvo PCR

Table 1. Case summaries.

Postnatal		
Neurologic	• Autism spectrum disorders • Intellectual disability/ developmental delay • ADHD • Hypotonia	• Seizures • Behavioral abnormalities (aggressive behavior, temper tantrums, impulsivity, compulsivity, stubbornness, manipulative behavior)
Other characteristics	• Dysmorphic facial features • Cardiac abnormalities • Contractures • Eye abnormalities (esotropia, myopia, strabismus, nystagmus)	• Hypogonadism • Short stature • Scoliosis • Abnormal MRI • Feeding difficulties • Sleep disturbance • Abnormal gait • Hearing difficulties • GERD

Prenatal
• Cystic hygroma • Cardiac abnormalities • Decreased fetal movement • Polyhydramnios • Contractures

Table 2. Previously reported phenotype.

Discussion

HAFOUS is a recently described neurodevelopmental disorder with limited data on presentation, especially in the prenatal period. We present 3 cases of fetal hydrops, which likely represents the most severe end of the HAFOUS clinical spectrum. While the exact disease mechanism is not known, *USP7* is involved in critical cellular pathways which are essential for normal fetal development. Expression of *USP7* is essential for normal MAGEL2 protein function and loss of function variants in MAGEL2 lead to Schaaf-Yang syndrome (SYS), which has overlapping neurodevelopmental phenotype. Both HAFOUS and SYS involve hypotonia, which can impair fetal movement and potentially lead to fetal akinesia or fetal hydrops. While we noted abnormal foot positioning in one fetus, the full description of prenatal phenotype was limited by the nature of the cases.

Conclusions

This report contributes to the mutational spectrum of *USP7*-related conditions. We present 3 fetal cases with the most severe end of the HAFOUS clinical spectrum reported to date. Variants affecting *USP7* noted on both exome and microarray should be considered in the differential diagnosis when fetal hydrops is diagnosed.

References

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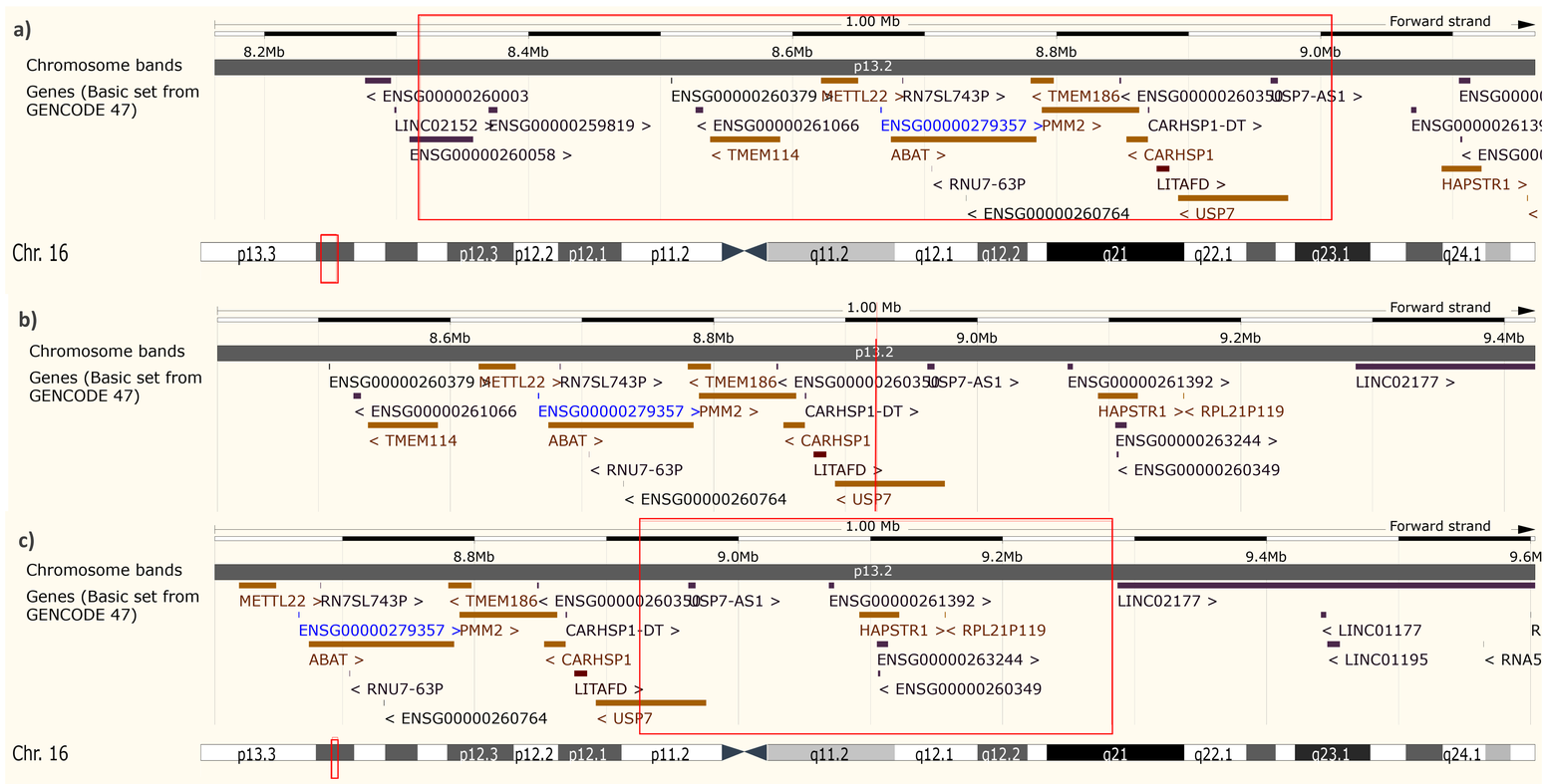

Figure 1. Location of variants: a) case 1 deletion; b) case 2 variant; c) case 3 duplication.