A maternally inherited novel variant in *USP9X* causing multiple congenital anomalies in a female fetus

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Background: Female-restricted X-linked syndromic mental retardation-99 (MRXS99F) is a neurodevelopmental disorder caused by heterozygous variants in the *USP9X* gene on Xp11. MRXS99F is characterized by delayed psychomotor development and intellectual disability (100%) with characteristic facial features. More than half of affected females also present with a wide range of additional congenital anomalies, including structural brain abnormalities, progressive scoliosis, hip dysplasia, postaxial polydactyly, heart defects, hearing loss, gastrointestinal and urogenital anomalies. To date, most literature reported MRXS99F patients have been identified with de novo variants. We report a female fetus with a novel, maternally inherited *USP9X* variant identified following termination of pregnancy.

Case Report: An abnormality of the posterior fossa was identified in a female fetus at 12 weeks gestation. The mother had a personal history of scoliosis and hearing loss. Follow-up ultrasound was consistent with a likely Dandy-Walker malformation, cardiac defect, and two vessel cord. Further imaging using fetal MRI, ultrasound, and fetal echocardiogram revealed additional abnormalities. The anomalies included Dandy-Walker malformation, mild ventriculomegaly, hypoplastic left heart syndrome, bilateral hand post axial polydactyly, kyphosis of the thoracic spine, and bilateral kidney pyelectasis. The pregnancy was subsequently terminated. Given the multiple abnormal imaging findings, an underlying genetic cause was highly suspected. Since the prenatal microarray was normal, the family was counseled about the option for Whole Exome Sequencing (WES) on products of conception and tissue was obtained at the time of the termination for WES on the POC.

Results: A maternally inherited heterozygous nonsense variant, c.643C>T (R215X), in *USP9X* was identified. This variant has not been reported previously nor has it been observed in population databases. R215X was interpreted as a pathogenic variant because it is predicted to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. Moreover, the clinical features of this case fit the description of this condition well.

Conclusion: R215X was interpreted as a pathogenic variant likely related to the clinical features reported in this fetus. However, the R215X variant was also present in the presumably mildly affected mother with scoliosis and hearing loss without dysmorphic features or intellectual disability. The presence of skewed X-inactivation or mosaicism in the mother would support the pathogenicity of the R215X variant. This case can also suggest that *USP9X* variants in females can have a wider spectrum of presentation than previously appreciated.