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Prenatal diagnostic testing challenges with novel gene alterations in KCNMA1-linked channelopathy: A case report

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I. Introduction

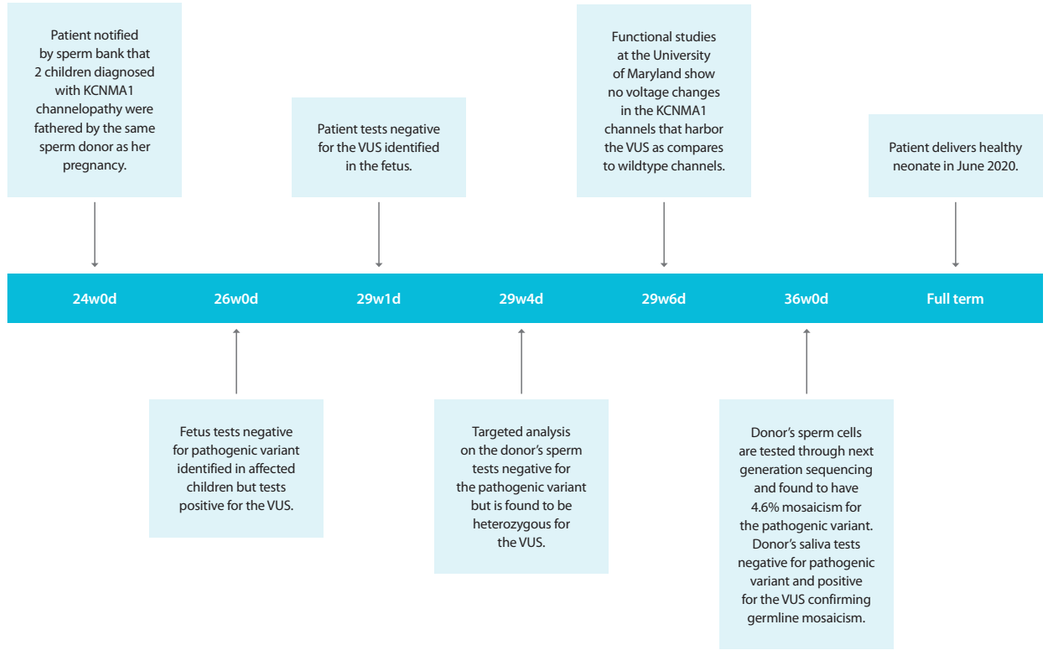
KCNMA1-linked channelopathies are rare conditions associated with a range of symptoms including developmental delay, paroxysmal dyskinesia (sometimes reported as cataplexy), and seizure disorders. Approximately 50 cases have been reported with nearly all being *de novo* with autosomal dominant inheritance. This case report illustrates the challenges of genetic counseling for novel candidate genes such as KNCMA1.

II. Case Overview

We report our experience with a 41-year-old woman, who presented during her first pregnancy, which was achieved with IVF and sperm donation (**Figure 1**). Her pregnancy had been uncomplicated and included a normal microarray analysis following chorionic villus sampling (CVS) performed on maternal request, and a normal detailed anatomical survey. At twenty-four weeks' gestation, the patient was notified by the sperm bank that two children, conceived from the same donor and two different mothers, had been diagnosed with KCNMA1-related channelopathy. Both children were found to carry a known pathogenic variant; p.N995S (c.2984 A>G), as well as a variant of unknown significance (VUS); p.R1128W (c.3382 C>T) in the KCNMA1 gene. Given that the mothers of these individuals were not related, these variants were presumed to be inherited from the sperm donor, who was reportedly unaffected. This could be explained by variable expressivity or germline mosaicism for the N995S variant. During genetic counseling, the patient requested that any additional available testing be performed to evaluate the potential for clinical implications in the fetus. Next generation sequencing of DNA saved from the CVS revealed that this fetus was negative for the N995S pathogenic mutation but was positive for the R1128W VUS. The patient had KCNMA1 testing for the R1128W VUS and was negative. Subsequent next generation sequencing on saliva from the sperm donor was negative for the N995S pathogenic mutation but positive for the R1128W VUS. Follow-up testing of the donor's sperm cells revealed 4.6% mosaicism for the N995S pathogenic variant, supporting the theory of germline mosaicism for the known pathogenic mutation.

The R1128W variant is present in ClinVar as a VUS based on a single submission. This variant has been previously reported in the literature from an individual harboring two KCNMA1 variants and neuromuscular dysfunction (Moldenhauer, et al 2020). During this pregnancy, functional KCNMA1 ion channel studies of the electrophysiological properties of the R1128W variant by itself were performed under a research protocol at the University of Maryland School of Medicine. No difference in the current-voltage relationships for R1128W channels compared to wildtype channels were found, suggesting that this gene alteration is functionally benign. The patient continued the pregnancy, giving birth to an apparently healthy full term neonate. The child is registered with the KCNMA1 channelopathy foundation (KCIAF.org) and will continue to be monitored throughout her development. The child and her biological father are the only known individuals with the R1128W variant present in all cells and without any known pathogenic variants in KCNMA1.

Figure 1. Timeline of case



III. Conclusions

This case demonstrates the complexity of prenatal genetic counseling when novel candidate genes are discovered and the benefits, when feasible, of testing genetic relatives as well as collaboration with researchers in providing clinically relevant information for patients. Furthermore, the fact that this pregnancy was achieved via sperm donation further complicates the potential for genetic testing. Based on the findings presented in this case, the R1128W variant, which is currently categorized as a VUS, may be considered for reclassification as a benign variant. This is supported by the functional channel studies and by presentation of the healthy living adult and child with the R1128W variant and no reported signs or symptoms of a KCNMA1 channelopathy.

IV. References

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