Sperm from a Patient with a Homozygous In-Frame Deletion in CATSPERE Lack Functional CatSper Expression and Fail to Fertilise at IVF

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Background: CatSper is a multi-subunit sperm-specific calcium channel that mediates the progesterone-induced increase in intracellular calcium. Evidence from CatSper subunit knock-out mouse models implicates it as essential for sperm fertilisation competence. Similarly, impaired or absent P4 response in patient sperm is associated with poor or loss of fertilisation at IVF. However, genetic evidence in a limited number of cases reported genomic deletions spanning a number of loci. We reported a unique case (Williams et al., 2014) of a man (patient 1) with sperm that lacked functional CatSper expression but he had no genetic errors in CatSper subunit coding regions. Subsequently, two new proteins have been proposed to be part of the mature complex (CatSper-epsilon and CatSper-zeta).

Main Questions: Does a patient with a reported defect in CatSper functional expression have a genetic defect limited to CatSper-epsilon and/or zeta?

Experimental Design: Exome data from patient 1 were analysed for genetic errors in CatSper-epsilon and CatSper-Zeta. Sanger sequencing was conducted to confirm the presence of a genetic defect.

Main Results: Patient 1 is homozygous for an in-frame 6-bp deletion in exon 18 (c.2393_2398delCTATGG, rs761237686) of CATSPERE that is predicted to be highly deleterious. Additional non-pathogenic intronic variations were also identified.

Conclusion: The reported mutation is the probable cause of loss of functional expression of CatSper in sperm from patient 1. However, further in vitro studies and population genetic analysis are necessary to confirm this hypothesis.

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