Teratozoospermia Caused by Mutation in Actin-like 7A

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Study question: What’s the etiology of severe teratozoospermia characterized as bubble-shaped acrosome (BSA)?

Summary answer: Severe teratozoospermia characterized as BSA caused by mutation (c.1024G>A) in actin-like 7A (ACTL7A).

What is known already: Teratozoospermia is a common cause of male infertility, defined by having a proportion of morphologically normal sperm at less than 4%. It exhibits aberrant sperm phenotypes in the head, neck, mid-piece, and endpiece of sperm. Teratozoospermia with ephalic abnormalities are among the most severe and characteristic sperm defects. Some genetic factors are reported to be associated with ephalic abnormalities such as globozoospermia and macrozoospermia. However, other phenotypes and the causative genes of ephalic abnormalities, especially in acrosomal structure, and were largely unknown.

Study design, size, duration: Severe teratozoospermia were recruited from the Reproductive and Genetic Hospital of CITIC-Xiangya from Jan 2019 to Dec 2021.

Participants/materials, setting, methods: Whole-exome sequencing analysis was used to analyze the genetic factor of man. An Act7a-mutated mouse model was generated by CRISPER-Cas9. Transmission electron microscopy was used to detect the abnormality of ultrastructure during acrosome biogenesis. Immunostaining was used to analyze the localization of ACTL7A and PLCγ. Immunoprecipitation followed by liquid chromatography-mass spectrometry (LC-MS) was used to select the differentially expressed proteins. ICSI with calcium ionophore exposure was performed in couple with ACTL7A mutation.

Main results and the role of chance: We found a man with severe teratozoospermia characterized as BSA carrying a mutation (c.1024G>A) in ACTL7A. Homozygous Act7a-mutated male mice were sterile, and all of sperm showed acrosomal abnormalities. During acrosomal biogenesis, it detected the acrosome detach from the nuclear in Act7a-mutated mice. Furthermore, mutant ACTL7A failed to attach to the acroplaxome and was discharged by cytoplasmic droplets, which led to the absence of ACTL7A in mature sperm. The mutant sperm failed to activate the oocyte, and PLCγ discharge accompanied by ACTL7A was observed, leading to total fertilization failure (TFF). Immunoprecipitation followed by LC-MS showed that several differentially expressed proteins participate in acrosome assembly and actin filament organization. Furthermore, assisted oocyte activation by calcium ionophore exposure successfully overcame TFF in a couple with an ACTL7A mutation.

Limitations, reasons for caution: More cases are needed to demonstrate the relationship between mutation and phenotype.

Wider implications of the findings: Our study defined a novel phenotype of the acrosomal abnormality characterized as BSA and revealed the underlying mechanism of mutation in ACTL7A and provided a genetic marker and a therapeutic option for male infertility.

Trial registration number: Not Applicable