Exploring QRICH2 as a Potential Male Contraceptive Target

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Currently, the contraceptive options available to men are limited to condoms and vasectomy. This highlights the pressing need for the development of alternative contraceptive methods. In this regard, identifying and characterizing reproductive tract specific proteins that can be targeted by natural or chemical compounds is crucial. We propose that QRICH2 could serve as a potential target as it appears to be testis-enriched and mutations (in humans and bulls) or knockout (in mice) of this protein result in complete infertility without evident accompanying symptoms (Shen et al. 2019, Nat. Commun. 10(1): 433; Kherraf et al. 2019, Clin. Genet. 96(5): 394–401).

The objective of this study is to better characterize human QRICH2 to determine if it could be used as a male contraceptive target. We examined QRICH2 expression in 10 different organs by immunofluorescence and by analyzing published proteomes and showed that the protein is restricted to the testes. It is expressed at the level of the nucleus across all germ cell stages, except in elongated spermatids and spermatozoa, where it localizes in the flagellum. It is also expressed around the nucleus in Sertoli cells. In silico studies revealed that QRICH2 lacks sequence homology with other human proteins and exhibits high conservation among mammals, particularly in its three functional domains (Glutenin hmw superfamily, SMC_N superfamily, and DUF4795), the functions of which remain unknown. We also established a protocol for extracting and analyzing native QRICH2 from human spermatozoa. Notably, only strong denaturing buffers (containing high concentrations of SDS or urea) allowed to extract the protein, suggesting its high stabilization in the flagellum, possibly through interactions with cytoskeletal proteins. Indeed, interactions between QRICH2 and AKAP3, AKAP4, ODF2, and TSSK4 have been reported in the literature. However, these proteins are likely just a subset of QRICH2 partners, and we are currently exploring all potential partners through yeast two-hybrid analysis.

Although QRICH2 is not a classic target for inhibitor molecules (i.e., not an enzyme or channel), molecules targeting its interactions with protein partners could potentially lead to inhibition of its function.