

THE MOUSE MODEL CANNOT BE USED FOR SOME FUNCTIONAL STUDIES OF PATHOGENIC GENE VARIANTS ASSOCIATED WITH HUMAN MALE INFERTILITY

Exome sequencing is typically the method of choice for identifying gene variants related to male infertility. Pathogenic variants are then confirmed using functional analysis in model organisms—typically mice. However, the use of the mouse model is not applicable for those genes that are not evolutionarily conserved between mice and humans. In this respect, more than 800 primate-specific genes have been found in the human genome, with a significant proportion of them primarily expressed in the testis (Shao et al 2019; *Genome Res.* 29, 682–696).

In a recent paper published in the *AJHG* (Liu et al. 2023; *Am J Hum Genet* 110:516-530), the authors have used whole-exome sequencing, to identify deleterious variants of X-linked *SSX1* in six unrelated men with asthenoteratozoospermia. Since *SSX1* is a gene expressed predominantly in the testis of primates (not in mice), the authors used a non-human primate model (cynomolgus monkey) and tree shrews for the genetic manipulation of *SSX1* and its subsequent phenotypic analysis of fertility.

On the one hand, the results obtained in mutant animals (cynomolgus monkey and tree shrews) were consistent with the phenotype observed in humans (reduced sperm motility and abnormal sperm morphology). On the other hand, testis RNA sequencing showed that *Ssx1* deficiency influenced multiple biological processes during spermatogenesis.

This study provides an alternative strategy for in vivo spermatogenic studies of pathogenic gene variants that cannot be achieved via the murine models. Besides, it also emphasizes the importance of using a multidisciplinary approach to dissect the genetic factors that contribute to male infertility.