Researchers identify first sex chromosome gene involved in meiosis and male infertility

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A team of scientists led by University of Pennsylvania veterinary researchers have identified a gene, TEX11, located on the X chromosome, which when disrupted in mice renders the males sterile and reduces female fecundity. This is the first study of the genetic causes of infertility that links a particular sex chromosome meiosis-specific gene to sterility.

As with mice, the TEX11 gene is also located on the human X chromosome. Given that disruption of TEX11 causes azoospermia, or non-measurable sperm levels in mice, mutations in the human TEX11 gene may be a genetic cause of infertility in men. Because men have only one X chromosome that they inherit from their mother and thus only one copy of the TEX11 gene, any mutation could theoretically lead to sterility. Like other X-linked disorders such as color blindness and muscular dystrophy, genetic mutation causing a son's infertility could be passed from his mother.

Researchers hypothesize that a screening of the TEX11 gene may provide a pre-birth diagnosis for infertility in men.

The study, published in the March issue of *Genes & Development*, also reports the first meiosis-specific factor ever found on the X chromosome. Meiosis is the process of cell division that produces gametes in both sexes. During meiosis, homologous chromosomes undergo pairing, synapsis, recombination and faithful segregation. Meiosis allows the exchange of genetic material between paternal and

maternal genomes to produce genetically diverse gametes (sperm or eggs). Therefore, defects in meiosis are a leading cause of both infertility and birth defects.

An estimated 15 percent of couples are affected by infertility worldwide, yet the genetic causes of male infertility remain largely unknown. For decades, conventional wisdom stated that the X chromosome had little to do with meiosis or infertility because the X chromosome is silenced during male meiosis. This thinking led to fertility studies that focused on the Y chromosome and autosomes.

In fact, Jeremy Wang, assistant professor in the Department of Animal Biology at the University of Pennsylvania's School of Veterinary Medicine, and his team revealed in an earlier study of mouse male germ cells that nearly one third of the germ cell-specific genes they identified are located on the X-chromosome.

Wang and his team found that sex chromosomes did play a role in meiosis. Although these X-linked, germ cell-specific genes undergo inactivation during later stages of male meiosis, they play a role in the early stages. Specifically, researchers found that TEX11 forms discrete foci on meiotic chromosomes and appears to be a novel constituent of the meiotic recombination machinery. The team genetically engineered male mice such that they lacked TEX11 function and found that this caused chromosomal asynapsis during the process of gamete formation.

This means that homologous chromosomes failed to pair together during meiosis and chromosomes formed fewer crossovers, i.e. sites where they recombine, during the initial stages of meiosis. These failures led to elimination of spermatocytes at later stages in the genetic recombination process and, ultimately, male infertility.

Researchers hypothesize that because TEX11 interacts with SYCP2, an

integral component of the protein complex that mediates synapsis during meiosis, TEX11 promotes both synapsis and genetic recombination and may provide a physical link between these two meiotic processes.

Source: University of Pennsylvania