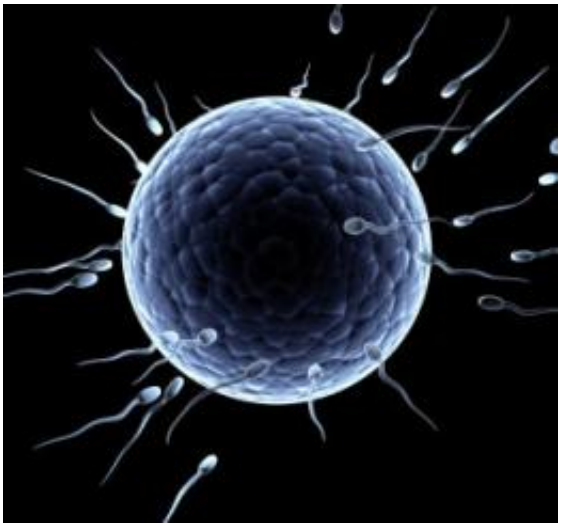
Genetic alteration linked with human male infertility

September 30 2010



One in seven couples worldwide has difficulty conceiving a child, and male infertility is thought to account for nearly half of those cases. Although the cause of male infertility is often unknown, scientists have now discovered a genetic alteration that disrupts sperm production in otherwise healthy men. The research, published by Cell Press on September 30th in the *American Journal of Human Genetics*, provides new insight into one cause of male infertility.

"Many genes are known to be essential for the production of sperm, but there are surprisingly few single gene changes that have been

conclusively demonstrated to cause a failure of sperm production in humans," explains senior study author, Dr. Ken McElreavey from the Pasteur Institute in France. Dr. McElreavey, along with co-authors Dr. Anu Bashamboo and Dr. John Achermann, a Wellcome Trust Senior Fellow from UCL Institute of Child Health London, examined whether the NR5A1 gene might be involved in some cases of male infertility.

The NR5A1 gene codes for a key protein called steroidogenic factor 1 that regulates fetal, prepubertal and adult sexual development. Previous work had shown that NR5A1 mutations are associated with severe defects in the development of the testes or ovaries as well as significant anomalies of the male external genitalia. Dr. McElreavey's group sequenced the NR5A1 gene in 315 healthy men seeking infertility treatment, who exhibited an unexplained failure to produce sperm.

"We identified seven men with severe failure to produce sperm who carried changes in the NR5A1 gene," says Dr. Bashamboo. The researchers went on to show that the mutations impaired the ability of the steroidogenic factor 1 protein to regulate the transcription of key reproductive genes. The mutations were associated with altered levels of sex hormones and, in the one case studied, mild abnormalities in the cellular structure of the testes. Similar genetic alterations were not observed in more than 2000 control samples.

These findings suggest that changes in NR5A1 are not just associated with severe and obvious defects in reproductive development. "We conclude the approximately 4% of men with otherwise unexplained failure to produce sperm carry mutations in the NR5A1 gene," says Dr. Bashamboo. "Our data also suggest that some forms of male infertility may be an indicator of a mild abnormality in testicular development, underlining a need for careful clinical investigation of men presenting with infertility and abnormal levels of sex hormones."

Provided by Cell Press