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Communiqué de presse

### **Male Infertility : Genetic Cause Identified**

**Scientists at the Institut Pasteur have identified a series of mutations in a gene that are associated with 4% of cases of, otherwise unexplained, severe male infertility. This discovery offers new opportunities not only in terms of an early diagnosis of male infertility associated with these mutations but also enables clinicians to provide counseling regarding the freezing of sperm or eggs to the couples concerned about procreation. Male infertility is a known risk factor for developing certain forms of cancer and this study reinforces the need for a long-term medical follow-up of patients carrying these mutations.**

Worldwide, one couple in seven is affected by infertility, and male factors can account for 30 to 50% of these cases. Although many genes are known to be essential for human germ cell development, there are surprisingly few single gene changes that have been conclusively demonstrated to cause a failure of sperm production in humans. Researchers at the Unit of Human Developmental Genetics at the Institut Pasteur directed by Ken McElreavey, have identified a gene whose mutations explain some severe cases of infertility in humans.

In 2009, the same team had already shown that mutations in the same gene, called *NR5A1*, could be the cause of ovarian insufficiency in women<sup>1</sup>. These studies led them to investigate the contribution of mutations in this gene in men with otherwise unexplained infertility.

The study, led by Dr. Bashamboo, investigated 315 men affected by unexplained infertility. The sequencing of the gene *NR5A1* for these individuals revealed seven mutations (4%) associated with severe spermatogenic failure. Similar mutations were not observed in more than 2000 control samples. This may be the most frequent single gene defect that is associated with male infertility known to date.

*In vitro* functional studies demonstrated a marked reduction in the biological activity of the mutant proteins as compared to the normal protein. The mutant proteins failed to adequately induce the expression of downstream target genes of *NR5A1*, that are known to be involved in the development of the testis and biosynthesis of certain testicular hormones.

This research has a direct medical impact. Some men carrying mutations show a progressive reduction in sperm quality and quantity over time. For the carriers of potentially pathogenic mutations in the gene it would be advisable to consider having children early in their reproductive lives or they may consider freezing their sperm.

Furthermore, some studies show that male infertility may be a risk factor for developing prostate or testicular cancer. In addition, mice that lack the *Nr5a1* gene also develop other diseases (hypertension, obesity etc.). It is therefore necessary to perform long term follow-up studies in men carrying *NR5A1* mutations to assess their risk of developing other diseases.

*This work was carried out in collaboration with AP-HP, Hôpital Tenon (Paris) and the Biological Resource Center GERMETHEQUE, which provided samples for the study. This was a collaborative study with a team from the University College London.*

<sup>1</sup> See our press communication of 26 February 2009 : [www.pasteur.fr/ip/easysite/go/03b-000030-02e](http://www.pasteur.fr/ip/easysite/go/03b-000030-02e)

## Source

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**Human Male Infertility Associated with Mutations in NR5A1 Encoding Steroidogenic Factor 1, *The American Journal of Human Genetics***, en ligne le 30 septembre 2010.

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