Geneticists crack the code of infertility

Nearly one out of every ten couples worldwide cannot conceive a child after trying for a year, according to recent epidemiological studies (*Hum. Reprod.* **22**, 1506–1512; 2007). The cause remains unknown among 25% of those with infertility. Now, new genetic studies suggest that, in some cases, the culprit might, in fact, lie hidden in one's DNA.

So far, scientists have identified nearly 300 DNA mutations in men with reproductive defects. When modeled in mice, many of these mutations have a pivotal role in the development of the ovaries, testes and especially sperm. Sperm and egg development starts with meiosis, a process in which chromosomes line up before self-segregating into daughter cells. During this process, pairs of chromosomes carry out an intricate cellular choreography of migrations and alignments to effectively swap genetic information.

If this gene-swapping action, known as 'recombination', goes awry, the resulting cells end up with either too few or too many chromosomes. When this produces aberrant sperm, they are usually eliminated through a process of biological checkpoints—in some cases causing men to produce semen with no sperm.

On the other hand, aberrant eggs containing the wrong number of chromosomes usually survive. But if one of these eggs is fertilized, the resulting zygote fails to develop normally, usually leading to miscarriage.

In 2000, Swedish scientists identified a protein, called synaptonemal complex protein-3 (Sycp3), that seems to facilitate the recombination process. Male mice lacking both copies of Sycp3 don't produce any sperm. And a follow-up study found that female mice that lack Sycp3 produce embryos with abnormal chromosome numbers that die *in utero*. In 2003, geneticists found *SYCP3* mutations in DNA samples from 2 out of 19 men who didn't produce sperm (*Lancet* **362**, 1714–1719; 2003).

Experts note, however, that most infertile men produce some sperm, but the sperm may not move well or may have abnormal shapes. For example, researchers found 28 infertile North African men who produced large-headed sperm that had up to four tails each instead of just one. Of these men, 23 had a mutation in the gene encoding aurora kinase C, which, like Sycp3, helps coordinate chromosome movement during meiosis.

The researchers say the aurora kinase C mutation is the first 'recurrent' mutation identified for male infertility, meaning that it gets passed down from generation to generation. They estimate that the original mutation occurred about 1,500 years ago.

Genetic screening procedures, though, may be futile: each specific genetic mutation only affects a fraction of the infertile, and methods to repair the genome are still a decade away.

"The trouble with genetics is it's always a very long time from when you identify the gene to the time you can do something for the patients," says Pierre Ray of Grenoble University Hospital, who presented the aurora kinase C results at the European Society of Human Reproduction and Embryology conference in Barcelona this past July. For the men with this mutation, "we tell them that the options are sperm donor or adoption," he says.

In fact, most of the identified genes come from samples this size or smaller, meaning that they don't come close to accounting for the number of people who are genetically infertile.

"If you look at the genes that have been analyzed so far, the frequency might be 1% in a fertile population and 4% or 5% in an infertile population," says Douglas Carrell, director of *In Vitro* Fertilization and Andrology Laboratories at the University of Utah School of Medicine. But he adds that most infertility probably stems from 'multiple hits' to the genome—an idea that only genome-wide scans of infertile men could test.

Therapy challenges

Researchers have had limited success in developing infertility treatments on the basis of gene therapy—replacing faulty genes with functional ones, usually with genetically engineered viruses.

Targeting the sperm or egg cells with gene therapy represents a huge challenge because they are tough to reach in the body. Instead, researchers are targeting defective genes in Sertoli cells, which produce growth proteins in the testes that nourish immature sperm. In 2002, researchers used an adenovirus to insert the mouse *Steel* (*Sl*) gene into Sertoli cells of infertile, *Sl*-knockout mice. The transgene was successfully taken up by the cells and partially restored spermatogenesis in the mice (*Proc. Natl. Acad. Sci. USA* **99**, 1383–1388; 2002).

Still, it's a long way from mice to humans. "Our limited understanding of the complex regulatory mechanisms underlying normal [sperm production] makes it difficult to identify specific target genes for gene therapy," says Yoshiyuki Kojima of Nagoya City University Graduate School of Medical Sciences, who also studies gene therapy in mouse Sertoli cells. He adds that it may be decades before the technology reaches the clinic.

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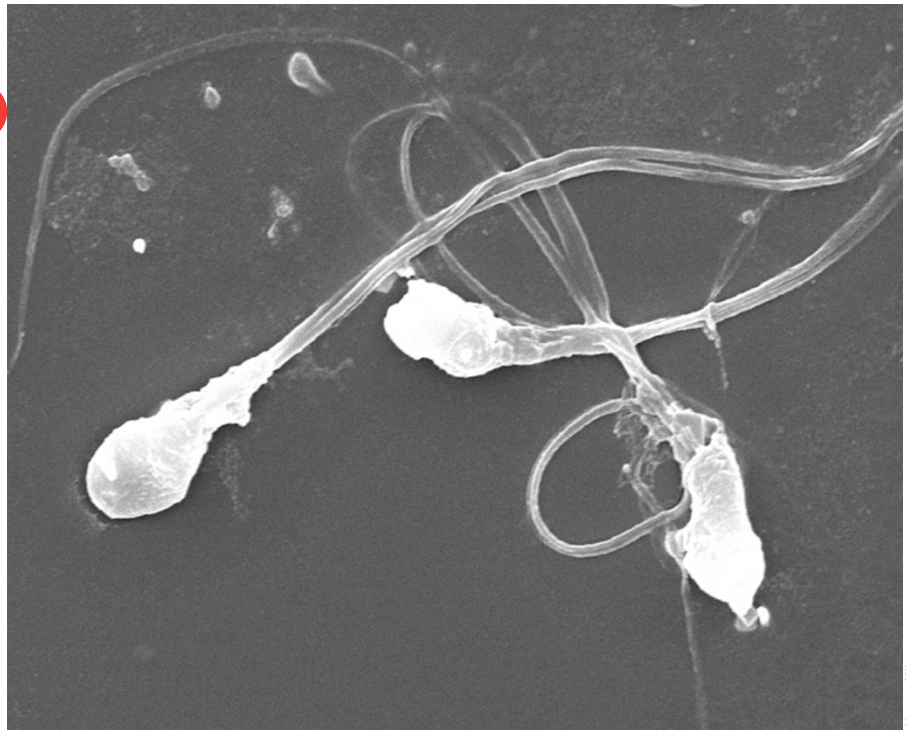

Yorgos Nikas

A four-tailed phenomenon: Specific genetic mutations explain these unusual sperm