Research on pigs may lead to answers for human male infertility

February 9 2009

In the late 1990s the Finnish Yorkshire pig population was threatened by a genetic defect which spread at an alarming rate and led to infertility. The defective KPL2 gene in porcine chromosome 16 caused pig spermatozoa to be short-tailed and immotile. The recessive genetic defect did not cause any other symptoms in the pigs.

Research Scientist *Anu Sironen* of MTT Agrifood Research Finland mapped the defective gene in her doctoral research. Sequence analysis of the candidate gene KPL2 revealed the presence of an inserted retrotransposon, a DNA sequence which moves around independently in the host genome. These transposable elements are found in all plants and animals.

Sironen also developed an accurate DNA test which can be used to identify animals carrying the defective gene with 100% certainty. The method, based on PCR technology, multiplies part of the KPL2 gene and detects the retrotransposon if it is present. The test has been used as a tool in Finnish pig breeding since 2006.

Human genome contains the same gene

Sironen's research also sheds light on the investigation of infertility in human males. KPL2 is, evolutively, an old gene that is present in all mammals and is similar in many species. The Line-1 retrotransposon which had inserted itself into this gene is present in the genome of all

mammals, including humans.

After Sironen had developed the genetic test for pigs, she continued researching the genetic defect mechanism in mice.

“The KPL2 gene appears to affect the formation of cilia, which are hair-like organelles projecting from cells. They are present in spermatozoa, but also in many other tissues, including the lungs and bronchial tubes. The cilia are able to sense the surrounding conditions and transmit signals to the cells,” she explains.

Besides infertility, genetic defects in the cilia may be linked to blood pressure regulation, tumor development, kidney diseases and obesity. A severe cilial defect leads to developmental failure at the embryotic stage.

Sironen points out that it has not yet been demonstrated whether a defective KPL2 gene causes infertility or other symptoms in humans. However, findings on its participation in the cilial development indicate this might be the case.

Gene defect may have other implications

Sironen observed that the insertion of the Line-1 retrotransposon into the KPL2 gene affects the gene expression, leaving the coded protein abnormally short.

The long form of KPL2 is expressed predominantly in the porcine testicular tissue, which explains the tissue-specificity of the defect. Sironen would like to investigate the functions of the gene in a broader context, to find out which tissues it operates in and what its role is in the formation of cilia elsewhere in the body.

Sironen is also interested to find out whether the insertion of Line-1

retrotransposon in the KPL2 gene has any positive impacts on the production traits of pigs. She points out that the retrotransposon can have multiple impacts in the genome: it can cause other genes to shift, or have an impact on the manifestation of neighbouring genes.

“The increase of the porcine short-tail sperm defect was alarmingly fast in the late 1990s. This implies that the genetic defect may have been associated with some positive genetic effect on the pigs’ production traits, which would explain why animals carrying the defect have been favoured in breeding,” says Sironen.

The doctoral thesis of Anu Sironen, M.Sc., entitled “Molecular genetics of the immotile short tail sperm defect”, will be publicly reviewed at the University of Turku on 20 February 2009.

Source: MTT Agrifood Research Finland