Discovery of new cause of mental retardation simplifies search for treatments

Two to three children in 100 are born with a mental handicap. This can be caused by a genetic defect, but in 80% of the cases scientists do not know which genes are responsible. Now, VIB researchers connected to the Katholieke Universiteit Leuven, in collaboration with an Australian research team, have discovered that, in a portion of these patients, the mental retardation is caused by a twofold production of two proteins (HSD17B10 and HUWE1).

This is the first time that scientists have found that duplication of a protein leads to mental retardation. The discovery offers promising possibilities in the search for remedies, because it's easier to reduce an over-production of a protein than to repair a defective protein or to replace a missing protein.

Defects on the X-chromosome

Mental retardation occurs in 2 - 3% of our population. This can be attributed to external factors (such as a shortage of oxygen at birth) or to defects in the DNA. When the cause is genetic (hereditary), identifying the precise defect is crucial for the patient's medical support or for assessing the risk of having children. Scientists estimate that, in about 30% of the patients, a defect on the X-chromosome is the underlying cause. This is called X-linked mental retardation (XLMR). In over half of the XLMR patients, the gene responsible has not yet been identified.

2 proteins in the leading role

Guy Froyen and his colleagues in the Human Genome Laboratory (VIB – K.U. Leuven) teamed up with Jozef Gécz's research group (University of Adelaide, Australia) to look for new genes that might lie at the basis of XLMR. With the aid of a very specialized molecular technology (X-chromosome specific array CGH), they studied the genes of some 300 XLMR families. In 6 of the families, they discovered that a certain part of the X-chromosome had been duplicated. Because of this duplication, two proteins, HSD17B10 and HUWE1, were produced in too high a concentration. The researchers in Leuven also found small alterations in both proteins in other XLMR patients. Through this research, they are uncovering the important role that these proteins play in the development of the brain's memory center.

A new mechanism opens possibilities

The VIB scientists' research is showing for the first time that the duplication of a chromosome region − whereby proteins are produced in too high a concentration − can lead to mental retardation. This is totally new information in the current understanding of genetic causes of mental retardation without attendant symptoms. Scientists have thought that defects that stop production of a protein, or cause it to be produced in a defective way, could lie at the basis of this disorder. The new discovery that too much of a protein can also cause mental retardation has a major impact on the quest for new therapies or medicines. Indeed, it's easier to scale back an over-production of a protein than to repair a defective protein.

Consequences for detecting and treating XLMR

The research being conducted by Guy Froyen and his colleagues presents new possibilities for detecting and treating XLMR. Tests can now be designed with which scientists can look for duplication of, and defects in, HSD17B10 and HUWE1. Developing a new treatment for XLMR, however, will require further research. Scientists must first gain greater insight into the role these proteins play in the body, and more

specifically, in the brain. Research models are now being set up for this effort.

Source: VIB (the Flanders Institute for Biotechnology)