IMBA Press Release

April 25, 2014

COVER STORY IN „CELL“ : NEW NEUROLOGICAL SYNDROME IN CHILDREN DISCOVERED

An international team including researchers from the Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences has found a new neurodegenerative syndrome in children that coincides with disorders of the brain and peripheral nervous system. It is caused by a mutation in the CLP1 gene. This is the first time the gene has been linked to human diseases.

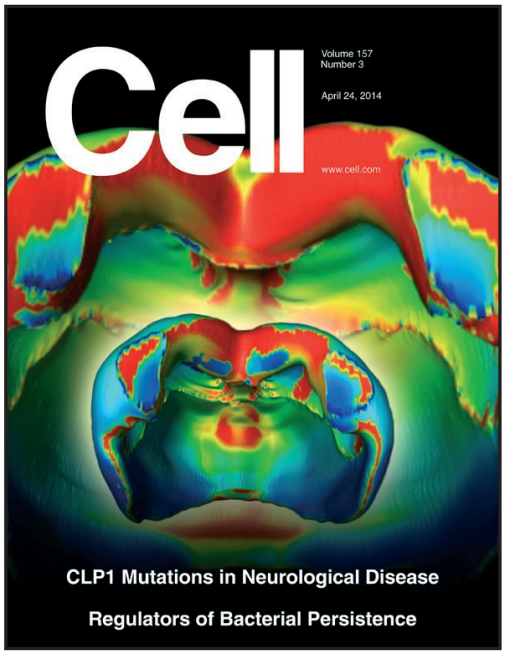
Last year IMBA scientists in the groups led by Josef Penninger and Javier Martinez discovered a mechanism in mice that causes the death of nerve cells. This mechanism is based on a genetic defect in the CLP1 gene, and is the cause of a number of neurodegenerative disorders involving myasthenia and paralysis, which often lead to death (Nature, 2013).

Genetic mutation in children – new syndrome

These events affected mice, but now researchers have found a mutation in the same gene in eleven children from five families. The children suffered from neurological disorders doctors were not able to specify. Under the leadership of James Lupski, scientists from Baylor College of Medicine in Texas sequenced the genome of the children. They discovered that the cause of the neurological disorders was a mutation in the CLP1 gene. Like the mice, the children with this genetic defect seemed to be „normal“ at birth. But soon sensory defects and disturbances in the function of their muscles became apparent.

In the children another symptom also occurred: microcephaly, a developmental disorder of the brain, which in this case was probably caused by the death of nerve cells in the brain. Their brains remained below average in size, and the children are mentally handicapped.

This is the first time the CLP1 gene has been linked to a human disease. The discovery of this new syndrome, which impairs both the brain and the peripheral nervous system, led to a cover story for the IMBA researchers and their colleagues in „Cell“, a renowned scientific journal.



CLP1, an IMBA success story

Javier Martinez, a group leader at IMBA, was the first person to discover the CLP1 gene (Nature, 2007). Last year his team, working with colleagues from Josef Penninger‘s laboratory, published findings that CLP1 mutations in mice led to muscular disorders and the death of nerve cells. But until this new study it was not yet known what role a CLP1 mutation plays in humans. „As we have now proved, the mechanism functions in a similar fashion in mice and humans. Once we know the signaling pathway in detail, we might then be able to intervene to repair the malfunction,“ said Martinez, a biochemist. Stefan Weitzer, a post-doctorate research fellow in the team of Martinez and one of the first authors of this study, explains the background: „A mutation in the CLP1 gene leads to disorders in the production of fully functional tRNA, which is essential for the generation of protein. The process that does not function correctly here is called „tRNA splicing“, and it affects the splitting and proper rejoining of RNA particles.“

ÖAW Austrian Academy of Sciences

IMBA Institute of Molecular Biotechnology of the Austrian Academy of Sciences

Uncommon inference: learning from people for mice

The scientists had not yet noticed the occurrence of microcephaly in mice. Hiroshi Shiraishi, one of the autors of the study, was surprised: „In more recent research we did actually find below-average sized brains in the animals as well." Research results on model organisms such as mice normally result in valuable insights for human medicine. In this case it was the other way around. For Josef Penninger, laboratory head and scientific director at the IMBA, this shows „how vital observations in humans are, because they often reveal previously unknown phenotypes (observable traits). With these insights, we then go back to the laboratory and investigate the genetic foundation. These in turn give us deeper insights into basic mechanisms of the development of the nerves and the brain that can later prove valuable in the treatment of diseases."

Proof of the „clan genetics" theory

At first there seemed to be no link among the five families of the children affected. But things became interesting when the researchers discovered that all eleven children had exactly the same genetic defect: it is impossible that precisely the same mutation can occur more than once by chance. That means that these children's ancestors must have been related many generations ago, but that their families were not aware of it. In fact, further investigation revealed that all the families' ancestors came from the same clan in Turkey. The discovery of this genetic mutation thus also supports the theory of „clan genetics", developed by researchers in the USA in 2011.

Original publication „Human CLP1 mutations alter tRNA biogenesis affecting both peripheral and central nervous system function", Karaca et al., Cell.

The scientific work was conducted in cooperation with scientists from the Baylor College of Medicine in Houston, Texas, under the leadership of James R. Lupski.