Scientists discover gene mutation responsible for hereditary neuroendocrine tumor

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University of Utah researchers and their colleagues have identified the gene that is mutated in a hereditary form of a rare neuroendocrine tumor called paraganglioma (PGL). The gene, called hSDH5, is required for activation of an enzyme complex that plays a critical role in the chemical reactions that take place within cells to convert biochemical energy into usable energy. This study will be published in the journal *Science*, to be released online in *Science Express* on July 23, 2009.

Paragangliomas are rare, generally benign tumors that arise from cells called glomus cells, which are located along blood vessels and play a role in regulating blood pressure and blood flow. Approximately 25 percent of paragangliomas are hereditary. Of the four familial PGL syndromes, three forms have previously been associated with mutations in genes of the succinate dehydrogenase (SDH) complex, an enzyme complex involved in the ability of cells to extract energy from nutrients.

Studies in Yeast

"Defects in mitochondria, the power sources of the cell, have been implicated in a variety of human disorders, including cancer," says Jared Rutter, PhD, associate professor of biochemistry at the University of Utah School of Medicine, investigator at the University's Huntsman Cancer Institute, and lead author of the study. "Because it is incredibly difficult to perform in-depth studies in humans, we decided to use a much simpler model system, the yeast Saccharomyces cerevisiae, in

order to study mitochondrial functions before going back to humans and determining whether what we learned in yeast was also relevant to humans. Following this strategy, we first characterized a mitochondrial protein called Sdh5 in yeast and then moved on to study its potential role in human disease."

Sdh5 is a mitochondrial protein that is highly conserved, meaning that it has remained largely unchanged throughout the course of evolution and likely performs similar essential cellular functions in both yeast and humans. Rutter and his colleagues discovered that, in yeast, the Sdh5 protein is needed for the SDH complex to function normally. They also found that Sdh5 is required for activation of another protein called Sdh1 that is also part of the SDH complex.

Studies in Humans

"The amino acid sequence of yeast Sdh5 is 44 percent identical to its human counterpart, which we've named hSDH5. This gave us some confidence that the Sdh5 functions we discovered in yeast would also be carried out by human hSdh5," explains Rutter. "Previous genetic studies have shown that the hereditary paragangliomas PGL1, PGL3, and PGL4 are associated with mutations causing loss of SDH activity. Although the gene for PGL2 had not been identified, we knew that it was located on the same chromosome as the hSDH5 gene."

Rutter and his colleagues sequenced the hSDH5 gene in three individuals with PGL2 from a previously described Dutch lineage. They identified a single DNA nucleotide change which resulted in a mutation in the most conserved region of the protein. Of the 45 individuals within the affected lineage who inherited the mutation, 33 have developed PGL2, providing strong evidence that hSDH5 is the PGL2 gene. The seven individuals who inherited the mutation from their mothers are unaffected, suggesting an inheritance pattern that is specific to the

parent of origin.

The researchers also discovered that, as in yeast, the inactivation of hSDH5 dramatically impaired the activity of the SDH complex, which was decreased by approximately 95% in tumors from three patients with PGL2.

Implications on Genetic Testing

The identification of hSDH5 as the PGL2 gene has potential clinical implications for patients with familial PGL syndromes. Genetic testing is suggested for the management of PGL, even when it does not seem to be inherited, in order to identify individuals who are at risk for developing tumors.

"Individuals with familial PGLs tend to be affected at a younger age with tumors at multiple sites," says Rutter. "Including hSDH5 in DNA screening will allow for more comprehensive genetic testing, as well as earlier detection and treatment."

Source: University of Utah Health Sciences (news : web)