Genetic mutation causes familial susceptibility for degenerative brain disease

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Mutation of a gene that helps proteins migrate in and out of the cell's genetic command center - the nucleus - puts some families at higher risk for the degenerative brain disease acute necrotizing encephalopathy (ANE).

This is the conclusion of a global study to be published Jan. 9 by the *American Journal of Human Genetics*, and currently posted online, that was led by a researcher from Cincinnati Children's Hospital Medical Center.

Researchers investigated cases where otherwise healthy children developed ANE soon after contracting common childhood infections like influenza A or parainfluenza. The study showed the children had mutations of the RANBP2 gene, which has multiple jobs in the cell. Other members of the children's families, which had histories of familial or recurrent ANE, also carried the same mutation, said lead investigator Derek E. Neilson, M.D., a physician/researcher in the division of Human Genetics at Cincinnati Children's.

Still unclear is just how the mutation leads to ANE in predisposed families and individuals, according to the research team, which included investigators from 30 institutions in the United States and overseas. The RANBP2 gene encodes the RANBP2 protein, which is located on the cytoplasmic surface of what's known as the nuclear pore. It helps the nuclear pore bring proteins into and out of the nucleus, regulates critical steps of cell division, modifies the chemical makeup of other proteins,

and interacts with components of energy production.

"This study opens new avenues of research, especially our unexpected finding that a missense mutation in part of the nuclear pore predisposes individuals to infection-triggered neurologic disease," said Dr. Neilson. "In order to prevent or lessen the neurological damage caused by ANE, it's very important to determine how missense mutations in RANBP2 predispose certain people to the disease."

The discovery also led the research team to recommend that ANE linked to mutation of RANBP2 be designated as ANE1. They also recommended that ANE1 and mutation of RANBP2 be considered in the differential diagnoses of patients showing symptoms consistent with ANE.

In a missense gene mutation, a single portion of the gene's DNA is reconfigured so that certain amino acids - which form the building blocks of proteins - are replaced, one for another. This change can remove a protein's function or, theoretically, set off biological chain reactions that lead to disease.

In the case of RANBP2, researchers still need to find out if mutation causes disease susceptibility by disrupting the protein's primary functions or whether it triggers a new chain of biological events. They suspect the latter and plan in future research to investigate how the mutation may impact the function of mitochondria. Mitochondria are the specialized parts of the cell that control energy production.

Mutation of RANBP2 is not the only susceptibility gene for the disease, although researchers said it accounted for 75 percent of the cases of familial or recurrent cases in the current study, showing up in 12 of 16 families. The gene mutation in itself is insufficient to cause full-blown ANE1. Additional genetic and environmental factors - such as the

specific biological route the virus takes and a person's nutritional status - may also be important considerations, the researchers said.

The study included nearly two hundred children and adults from 35 unrelated families, 50 of whom had confirmed episodes of ANE. Nineteen patients of European, Asian or African descent had isolated cases of ANE. None of the participants with isolated ANE, as well as over a thousand healthy control patients, carried the RANBP2 mutation. The rest of the participants came from 16 families of European descent affected by familial or recurrent forms of the disease.

In one family central to the current study, 16 family members had clinical symptoms of ANE. Presence of the disease was confirmed through pathologic examination of two children who died from their illness. About half of the family members also carried the gene mutation. Of those, slightly less than half had a previous episode of ANE, and about half of the individuals who became ill had recurrent ANE, the researchers said.

ANE was initially found in Asia and is now known to affect children worldwide. Cases in the United States are thought to be under-reported, Dr. Neilson said. The disease is known for causing neurologic injury in children following common infections, like flu. According to the U.S. Centers for Disease Control, the disease includes lesions of the brain and brain stem. The disease progresses rapidly with symptoms that include cough, vomiting and diarrhea in combination with neurologic dysfunction, alteration of consciousness and seizures. The disease is often fatal, or it can lead to long-term health problems for surviving patients.

Source: Cincinnati Children's Hospital Medical Center