Scientists discover gene mutation that causes children to be born without spleen

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The spleen is rarely noticed, until it is missing. In children born without this organ, that doesn't happen until they become sick with life-threatening bacterial infections. An international team of researchers led by scientists from Rockefeller's St. Giles Laboratory of Human Genetics and Infectious Diseases has now identified the defective gene responsible for this rare disorder. The findings, reported today in *Science Express*, may lead to new diagnostic tests and raises new questions about the role of this gene in the body's protein-making machinery.

Medically known as isolated congenital asplenia (ICA), this condition has only been officially documented in less than 100 cases in the medical literature. Alexandre Bolze, a visiting student in the St. Giles lab, headed by Jean-Laurent Casanova, set out to identify the gene responsible for ICA. He and his colleagues conducted an international search for ICA patients, and identified 38 affected individuals from 23 families in North and South America, Europe and Africa.

Bolze and his team sequenced 23 exomes – all DNA of the genome that is coding for proteins – one from each family. After filtering two public databases of genetic information for gene variations in controls, the researchers were left with more than 4,200 possible genes. To narrow this list of candidate genes further, Bolze hypothesized that the disease-causing gene would be more frequently mutated in the ICA exomes compared to control exomes. He then compared the exome sequences of the 23 ICA kindreds with exomes sequenced in the Casanova lab from 508 patients with diseases other than those caused by bacterial

infections. After applying statistical algorithms, Bolze found one gene with high significance: RPSA, which normally codes for a protein found in the cell's protein-synthesizing ribosome.

"These results are very clear, as at least 50 percent of the patients carry a mutation in RPSA," says Bolze. "Moreover, every individual carrying a coding mutation in this gene lacks a spleen."

The findings, Bolze says, are surprising because the ribosome is present in every organ of the body, not just the spleen. "These results raise many questions. They open up many research paths to understand the specific role of this protein and of the ribosome in the development of organs in humans."

More information: "Ribosomal Protein SA Haploinsufficiency in Humans with Isolated Congenital Asplenia," by A. Bolze, *Science*, 2013.

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