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Researchers identify cause of rare syndrome consistent with Fanconi Anemia

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An international team of researchers has established the cause of rare syndrome consistent with Fanconi Anemia: a de novo mutation in a so called RAD51 gene, which is responsible for repairing damages in the DNA. Fanconi Anemia is a chromosome instability disorder which occurs in one of around about 350,000 new born children. It is clinically typified by susceptibility to bone marrow failure, leukemia, different types of solid tumors and a strongly reduced life expectance of the affected persons. The investigators at the Institute of Systems Biology (ISB, Seattle), Free University Medical Center (VUMC, Amsterdam), and the Luxembourg Centre for Systems Biomedicine (LCSB) at the University of Luxembourg in collaboration with several other institutions in the United States and Europe have just published their results in the journal Nature Communications (DOI: 10.1038/ncomms9829).

For their investigations, the researchers used advanced whole genome sequencing as well as other cell and molecular biology techniques. "This way we identified a mutation in the so called RAD51 gene, "says Dr Patrick May of the LCSB´s Bioinformatics Core research group at the University of Luxembourg and there a driving force in the collaborative project. RAD51 is responsible for repairing damages in the DNA which occur regularly during cell proliferation.

The team made its findings in a child affected by Fanconi Anemia - with healthy parents and a healthy sister. "The particular mutation in this patient was a surprise to us," says Patrick May: "It occurred only in one of the two RAD51 gene copies, which every person carries in the genome, but every RAD51 gene copy was normal in the child´s parents." The scientists´ conclusion: The examined patient is carrier of a not inherited but a novel and in the same time dominant mutation. Until this case, the state of scientific knowledge was that mutations leading to Fanconi Anemia showed recessive inheritance and therefore had to be derived from both parents to lead to Fanconi Anemia. Spontaneous mutations of the RAD51 gene like in this case were not observed so far. "In consequence the protein with the altered amino acid sequence due to the mutation interfered with the activity of the normal protein," says May. "This are the reasons why the child is affected by Fanconi Anemia although his or her relatives are not carrier of the mutation."

This finding has implications for genetic counseling of families with a high risk for Fanconi Anemia. Until now people who wanted to become parents and who had relatives suffering from Fanconi Anemia were screened if one of the 17 genes connected with the disease showed a mutation. Now the risk of having a sick baby has to be recalculated. "Furthermore, understanding this mutation teaches us more about how the RAD51 gene product protects the DNA and how disruptions of DNA repair may lead to leukemia and solid tumors," says Patrick May. "Of course, understanding the origins of human cancer will help us diagnose it with more confidence earlier and devise new therapies to prevent or mitigate it. We could also support a yet weak association between Fanconi Anemia and mental retardation and neurodevelopment involving mutations in proteins of the downstream branch of the Fanconi Anemia DNA repair pathway, like shown before for a gene called BRCA1 and now in this study for RAD51."

Source:
University of Luxembourg