Infant's mysterious death leads to discovery of a family disease

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Erik Drewniak

(Medical Xpress)—Shortly after the death of his newborn son, 43-year-old Erik Drewniak was hospitalized with some of the same symptoms that killed the infant—high fever, severe respiratory distress, and hemorrhaging in the lungs, intestines, and brain.

Infectious agents had been ruled out in both cases. Doctors at Yale-New Haven Hospital asked: Could the Fairfield man's condition be related to the mysterious illness that took his 23-day-old son?

Researchers at the Yale School of Medicine have provided a definitive answer to the mystery. A genomic analysis of the Drewniak family published online Sept. 7 in the journal *Nature Genetics* reveals that Erik and his son—as well as another of Erik's sons—share a previously undescribed disease featuring dangerous spikes in temperature and inflammation. The study shows that the disease is caused by a mutation resulting in abnormal activation of a pathway normally triggered by bacterial invasion of cells.

"This is a great example of what we can do at Yale, seamlessly combining incisive clinical observation with genome sequencing, computational analysis, and biochemistry," said Richard Lifton, Sterling Professor of Genetics and co-senior author of the paper.

Dr. Neil Romberg, assistant professor of pediatrics and first author of the study, first saw the infant boy at Yale-New Haven Hospital shortly before his death and recognized the signs of a primary inflammatory disease, which was a key to identifying the causative mutation. "This study highlights the utility of genome sequencing in establishing a diagnosis for patients with unexplained illnesses," he said.

The Yale researchers used high-throughput DNA sequencing at the Yale Center for Genome Analysis to determine the sequence of all 21,000 protein-coding genes in the genome in members of the family. Within six days, researchers had come up with a provisional diagnosis. Erik Drewniak had a new protein-altering mutation that was absent in his own parents and was transmitted to his sons. Armed with this knowledge, doctors devised a treatment plan that eventually led to Drewniak's release from the hospital.

Biochemical analysis later comfirmed that the mutated protein caused activation of inflammation in the absence of infection. Markers of inflammation were chronically elevated in mutation carriers but not

other family members. In retrospect, Drewniak noted that he suffered from a similar severe undiagnosed illness at birth and has subsequently had high fevers induced by stress or fatigue his entire life.

"It is tragic that we were unable to save the baby, but grateful that his illness led to diagnosis of his father and brother," added Dr. Barbara I. Kazmierczak, associate professor of medicine and co-senior author of the paper. "Moreover, because there is an approved inhibitor of the inflammatory cascade caused by this mutation, this finding has therapeutic implications for other patients found to have this rare disease."

More information: Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation, *Nature Genetics* (2014) DOI: 10.1038/ng.3066

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