Researchers solve mystery surrounding the death of two sisters nearly 50 years ago

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Researchers at Mount Sinai School of Medicine have identified the genetic cause of a rare and fatal bone disease by studying frozen skin cells that were taken from a child with the condition almost fifty years ago. Their study, which details how the MT1-MMP gene leads to the disease known as Winchester syndrome, appears in the August 23, 2012 online edition of The *American Journal of Human Genetics*.

In 1969, Patricia Winchester, MD, a pediatric radiologist in New York City, was asked to diagnose two young sisters who were losing bone in their hands and feet, developing severe arthritis in their fingers and losing movement of their shoulders, elbows, hips and knees because of osteoporosis. The frozen skin cells that were recently studied by principal investigator, John Martignetti, MD, PhD, and his team of researchers in the Department of Genetics and Genomic Sciences at Mount Sinai, had been taken from one of the sisters. Ultimately, the disease rendered the girls incapable of moving without assistance, and proved fatal.

The cause of the disease has remained unknown until now, when the study's lead authors, post-doctoral students, Rebecca Mosig, PhD and Brad Evans, PhD, zeroed in on the MT1-MMP gene.

"This gene encodes an enzyme that needs to be specifically positioned on the membranes of cells to function correctly," explains Dr. Martignetti. "What we discovered is that these girls had a gene mutation which resulted in incorrect shuttling of the protein. Instead of being directed to

the cell surface where it could interact with the outside environment, the mutant protein never reached its final, correct destination and remained trapped in the cell's cytoplasm. Mislocalized, it lost its ability to function and the children developed severe arthritis and bone The enzyme lost its ability to interact with another disease-casuing protein, MMP-2. Dr. Martignetti's team had previously identifed mutations in the MMP-2 gene as the cause of a similar group of bone disorders in children.

The researchers says this recent discovery should provide diagnostic clarity and insight into possible treatments for children with Winchester syndrome, and other bone disorders, and for people in the general population who have osteoporosis and arthritis.

Provided by The Mount Sinai Hospital