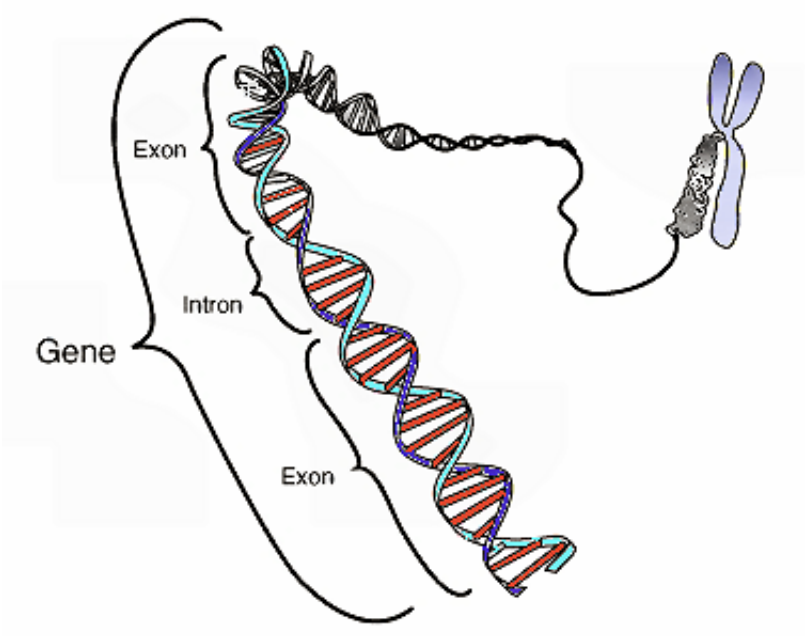
New genetic syndrome found, tied to errors in 'master switch' during early development

March 2 2015



This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

Analyzing a puzzling multisystem disorder in three children, genetic experts have identified a new syndrome, shedding light on key biological processes during human development. The research also provides important information to help caregivers manage the disorder, and may offer clues to eventually treating it.

"This syndrome illuminates a very important pathway in early human

development—a sort of master switch that controls many other genes," said study leader Ian D. Krantz, M.D., co-director of the Individualized Medical Genetics Center at The Children's Hospital of Philadelphia (CHOP). Krantz, a medical geneticist, is an attending physician in CHOP's comprehensive human genetics program.

Krantz is the senior author of the study, published online today in *Nature Genetics*. His co-study leader is Katsuhiko Shirahige, Ph.D., of the Institute for Molecular and Cellular Biosciences, University of Tokyo, also the home institution of first author Kosuke Izumi.

The investigators named the disorder CHOPS syndrome, with the acronym representing a group of symptoms seen in the affected children: cognitive impairment and coarse facies (facial features), heart defects, obesity, pulmonary involvement, short stature and skeletal dysplasia (abnormal bone development).

The central research finding is that mutations in the gene AFF4 disrupt a crucial group of proteins called the super elongation complex (SEC). The SEC controls the transcription process by which DNA is copied into RNA, enabling genes to be expressed in a developing embryo. The timing of this biological process is tightly regulated, so anything that interferes with this timing can disturb normal development in a variety of ways.

"Because the SEC involves such a crucial process in cell biology, it has long been a focus of study, particularly in cancer," said Krantz. "CHOPS syndrome is the first example of a human developmental disorder caused by germline mutations in the SEC."

Originating in the embryo, germline mutations are passed along to every cell in a developing organism, with harmful effects in multiple organs and biological systems. The mutated AFF4 gene produces mutated

proteins, which then accumulate and cause a cascade of abnormalities in other genes controlled by AFF4.

"AFF4 has a critical role in human development, regulating so many other genes," said Krantz. "When it is mutated, it can damage the heart and skeleton, and lead to intellectual disability, among other effects."

The current study sequenced the exomes (the protein-coding portions of DNA) of three unrelated children treated at CHOP for a complex developmental disorder. All three patients had some symptoms similar to those found in patients with Cornelia deLange syndrome (CdLS), a rare multisystem disease long studied at CHOP. Krantz led research that discovered the first causative gene for CdLS in 2004.

The research team's DNA analysis and studies of gene expression patterns determined that the new syndrome is genetically distinct from CdLS, even while sharing some common molecular mechanisms. Although only the three children in the study are known to definitely have CHOPS syndrome, Krantz expects diagnoses to increase with the dissemination of this discovery and the ongoing spread of faster, lower-cost gene-sequencing technology.

The research findings offer practical and emotional benefits for families, said Krantz. Physicians may now order more appropriate tests to monitor and manage specific medical issues arising from CHOPS syndrome. "This also means families and children can end their 'diagnostic odyssey'—the frustrating procession of tests and unsuccessful treatments that often occurs in trying to find an answer for families who have a child affected by a complex, undiagnosed disorder," he added.

The researchers have shown that CHOPS syndrome is a de novo condition—being caused by a new mutation arising in a single egg or sperm that went on to form the affected child, but not present in the

patient's parents. Therefore, doctors can reassure parents that this illness is extremely unlikely to recur in any subsequent children.

Like many other rare genetic diseases, CHOPS syndrome does not yet have an effective treatment; physicians like Krantz can only manage the symptoms. But the research team's insight into the basic biology of this disorder may lay the groundwork for future treatments of this disease, and possibly others.

More information: "Germline Gain-of-Function Mutations in AFF4 Cause a Developmental Syndrome Functionally Linking the Super Elongation Complex and Cohesin," *Nature Genetics*, published online March 2, 2015. doi.org/10.1038/ng.3229

Provided by Children's Hospital of Philadelphia