Gene discovered for Weaver syndrome

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Scientists have found a gene that causes Weaver syndrome, a rare genetic disorder that typically causes large size at birth, tall stature, developmental delay during childhood, and intellectual disability. Published today in the *American Journal of Human Genetics,* the discovery means that testing the EZH2 gene for mutations could help families who are seeking a diagnosis for their child.

"For the families among whom we identified the gene, this discovery definitively brings the diagnostic odyssey to a close – it's DNA confirmation that their children have Weaver syndrome," says Dr. William Gibson, the study's lead investigator. Dr. Gibson is a clinician scientist at the Child & Family Research Institute at BC Children's Hospital and an assistant professor in the Department of Medical Genetics at the University of British Columbia (UBC).

"Our discovery enables DNA-based diagnostic testing for this particular disease," says Dr. Gibson. "For physicians who suspect Weaver syndrome in one of their patients, we can now confirm it if we find mutations in EZH2. There may still be other Weaver syndrome genes, and we need to study more families to be sure."

Presently, doctors diagnose Weaver syndrome by assessing a child's face, growth, skeleton and other clinical features. People with Weaver syndrome have an oversized head, typical facial features, problems with muscle tone and joints, and differences in the way their skeleton matures. Mutations in the NSD1 gene, which normally causes a rare disease called Sotos syndrome, are also known to cause Weaver

syndrome in some cases. There may be other genes involved in Weaver syndrome that are yet to be discovered.

"Now we have an answer for these families and we are also in a position to provide answers to other families affected by this rare and difficult disease," says Dr. Gibson. He is available to see new patients clinically for diagnosis of Weaver syndrome. As a result of this discovery, Dr. Gibson's team now offers sequencing of the EZH2 gene on a research basis in partnership with the Ottawa Hospital Research Institute. Dr. Gibson's team can be contacted by email at wtgibson@cfri.ubc.ca.

Traditionally, hunting for a disease-causing gene has relied on tracking a gene throughout a family's history. However, Weaver syndrome usually occurs only once in a family, as it is thought to be caused by a new genetic mutation in the sperm or egg that conceived the child. For this study, the investigators sought patients with Weaver syndrome from Canada and the United States. They approached Dr. David Weaver, who discovered the syndrome in 1974 and is professor emeritus of Medical and Molecular Genetics at Indiana University School of Medicine in Indianapolis. In two families that Dr. Weaver had examined, the Canadian team looked for brand new genetic mutations by comparing the DNA of affected children to DNA from their unaffected parents. Once the investigators identified EZH2 as a candidate gene, they sequenced it in DNA samples from a third Canadian family. They confirmed that an EZH2 mutation was in this third family's child but not in either of her healthy parents.

EZH2 is a cancer gene that is known to be mutated in leukemia, B-cell lymphomas and some other blood cancers. The gene helps control how DNA is packaged around specific proteins, which in turn helps to regulate which groups of genes are turned off and on.

"Our finding illuminates an emerging area of biology that links

developmental syndromes and cancer," says Dr. Gibson. "It appears that some mutations in EZH2, if these occur early in life, produce developmental syndromes such as Weaver syndrome, whereas mutations in the same gene that occur later in life can produce cancer."

Dr. Steven Jones is the study's senior author who led the DNA sequencing and bioinformatics. He is head of bioinformatics and associate director of the Michael Smith Genome Sciences Centre at BC Cancer Agency, professor in the UBC Department of Medical Genetics, and professor, Molecular Biology & Biochemistry at Simon Fraser University (SFU).

Provided by Child & Family Research Institute