THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

EZH2 analysis for Weaver Syndrome

Clinical Features:

Individuals with Weaver Syndrome [OMIM #277590] are characterized by pre- and postnatal overgrowth with marked macrocephaly, advanced bone age, developmental delay and characteristic facial features (1). The Weaver syndrome phenotype overlaps with Sotos syndrome [OMIM #117550] and the two syndromes may be difficult to differentiate from one another. Clinical features shared by both syndromes include developmental delay, and overgrowth with prominent macrocephaly. Distinguishing features of Weaver syndrome include facial features such as broad forehead and face, ocular hypertelorism, prominent wide philtrum, micrognathia and deep horizontal chin groove. Weaver syndrome patients also tend to have deep-set nails and advanced carpal bone development compared to Sotos syndrome with normal or regressed carpal bone development (2).

Molecular Genetics:

Mutations of the *EZH2* [OMIM #601573] gene have been identified in patients with Weaver syndrome. Exome sequencing revealed heterozygous missense and frameshift mutations in the *EZH2* gene in several unrelated patients with Weaver syndrome (2, 3). In addition, subsequent Sanger sequencing of *EZH2* in 300 additional patients with Weaver syndrome or a non-specific overgrowth syndrome identified 15 additional mutations (missense, nonsense and frameshift) (3). *EZH2* has 20 coding exons and plays a role in stem cell maintenance and cell lineage determination. Somatic gain-of-function mutations in EZH2 have been reported in haematological malignancies, thus EZH2 mutations may confer a mild predisposition to malignancy (2).

Inheritance:

EZH2 mutations are inherited in an autosomal dominant pattern, although most cases appear to be *de novo.* Recurrence risk for affected individuals and carrier parents is 50%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

EZH2 sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
Turn-around time:	4 weeks

EZH2 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

EZH2 mutation analysis (sequencing and del/dup analysis)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube

Cost:	$1700
CPT codes:	81405, 81406
Turn-around time:	8 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Weaver DD, Graham CB, Thomas IT et al. A new overgrowth syndrome with accelerated skeletal maturation, unusual facies, and camptodactyly. J Pediatr 1974: 84: 547-552.
2. Gibson WT, Hood RL, Zhan SH et al. Mutations in EZH2 cause Weaver syndrome. Am J Hum Genet 2012: 90: 110-118.
3. Tatton-Brown K, Hanks S, Ruark E et al. Germline mutations in the oncogene EZH2 cause Weaver syndrome and increased human height. Oncotarget 2011: 2: 1127-1133.

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