

# The University of Chicago Genetic Services Laboratories



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## 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:

We offer mutation analysis of all coding exons and intron/exon boundaries of *EZH2* by direct sequencing of amplification products in both the forward and reverse directions. Deletion/duplication analysis 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 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1500
CPT codes:	81406
Turn-around time:	4-6 weeks

#### EZH2 deletion/duplication analysis

Sample specifications:	3 to 10 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.**

#### Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	81403
Turn-around time:	3-4 weeks

### Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	\$540
CPT codes:	81403
Turn-around time:	1-2 weeks

### **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.

### **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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