Kleefstra Syndrome: *EHMT1* Gene Deletion/Duplication

**Test Code:** JP  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

## Condition Description

Kleefstra syndrome, also known as chromosome 9q subtelomere deletion syndrome (9qSTDS), is among the first and most common clinically recognizable syndromes to arise from widespread testing by fluorescent in situ hybridization (FISH) of subtelomere deletions. There are about 50 reported cases worldwide.

Affected individuals invariably have severe hypotonia with speech and gross motor delay. The facial gestalt is distinct and features:

- Absolute/relative micro- or brachycephaly
- Hypertelorism
- Synophrys and/or arched eyebrows
- Mid-face hypoplasia
- A short nose with upturned nares
- A protruding tongue with exverted lower lip and down-turned corners of the mouth.

Approximately half of affected individuals have congenital heart defects (primarily ASD/VSD). A significant minority have epilepsy and/or behavioral and sleep disturbances. A variety of other major and minor eye, ear, genital, and limb anomalies have been reported.

Most patients have sub-microscopic deletions of the subtelomere region of chromosome 9q34.3 that range from 400kb - 3Mb. Kleefstra syndrome is caused by haplo-insufficiency of the *EHMT1* gene whose protein product (Eu-HMTase1) is a histone H3 Lys 9 (H3-K9) methyltransferase. This was established by identification of three patients with features of the syndrome and either mutations or a balanced translocation in *EHMT1*. H3-K9 histone methylation is restricted to the euchromatin of mammals and functions to silence individual genes. Deletion size does not correlate with the severity of Kleefstra syndrome, since patients with mutations in *EHMT1* are as severely affected as those with submicroscopic deletions.

Patients clinically suspected of having Kleefstra syndrome, but with normal subtelomere deletion testing by FISH or MLPA, should be considered for detailed deletion/duplication analysis and/or sequencing of *EHMT1*.

*EHMT1* is another example in the growing list of genes responsible for brain development that appear to play a role in chromatin remodeling. (Taken from Stuart, D and Kleefstra, T. The chromosome 9q subtelomere deletion syndrome. Am J Med Gen C Semin Med Gen. 2007 Nov 15;145(4):383-92.)

Deletion/Duplication testing should be ordered as the first tier test.

## Genes

*EHMT1*

## Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Kleefstra syndrome.

## Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

## Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

## Specimen Requirements

Submit only 1 of the following specimen types

**Type:** DNA, Isolated

**Specimen Requirements:**
- Microtainer
- 3µg
- Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.
Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Special Instructions

Related Tests

- Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Sequence analysis of the EHMT1 gene is available for those individuals in whom deletion/duplication analysis is negative.
- Prenatal Custom Diagnostics is available for known familial mutations only. Please call the laboratory genetic counselor before collecting a fetal sample.