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.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**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

* Preferred specimen type: Whole Blood

**Type:** Whole Blood
Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**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.