## Condition Description

Kleefstra syndrome, also known as 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 9q deletion/duplication analysis and/or sequencing of *EHMT1*. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array.

*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

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

### Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

### Specimen Requirements

*Submit only 1 of the following specimen types*
Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

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 24 hours of collection. Do not refrigerate or freeze.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™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.

Special Instructions

Related Tests

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