ZMPSTE24-related Disorders: ZMPSTE24 Gene Deletion/Duplication

**Condition Description**

Mutations in the ZMPSTE24 gene (1q24) can cause lethal restrictive dermopathy or mandibuloacral dysplasia.

**Lethal Restrictive Dermopathy**

Lethal restrictive dermopathy is an autosomal recessive type of fetal akinesia or hypokinesia deformation sequence (FADS). FADS is characterized by intrauterine growth retardation, congenital limb contractures, pulmonary hypoplasia, craniofacial abnormalities, and hydramnios. In lethal restrictive dermopathy, premature delivery and neonatal death are preceded by a reduction in fetal movement or fetal immobility. Additional features include thin, translucent, tightly adherent skin with prominent vessels, characteristic facies, bone mineralization defects, and an enlarged placenta with a short umbilical cord. Histologically, skin abnormalities include thin dermis and abnormally dense collagen bundles with absent elastic fibers.

Mutations in the ZMPSTE24 gene (1q24) or the LMNA gene can cause lethal restrictive dermopathy.

The ZMPSTE24 protein is involved in processing of the Lamin A protein precursor. In individuals with ZMPSTE24 mutations, abnormal ZMPSTE24 and Lamin A proteins can be seen. Please note that this test is only for the ZMPSTE24 gene.

**Mandibuloacral Dysplasia**

Mutations in the ZMPSTE24 gene and the LMNA gene also cause mandibuloacral dysplasia (MAD). MAD is an autosomal recessive heterogeneous progeroid syndrome. Features include craniofacial anomalies such as mandibular hypoplasia, dental overcrowding, bird-like faces, and thin beaked nose; skeletal anomalies; skin anomalies; stiff joints; post-natal growth delay; lipodystrophy; and normal intelligence. Individuals with MAD caused by mutations in the ZMPSTE24 gene tend to have a more severe phenotype than those with mutations in the LMNA gene. Many of the features appear before the age of 2 and are progressive. As is the case in lethal restrictive dermopathy, MAD due to ZMPSTE24 mutations causes abnormal unprocessed Lamin A protein to accumulate.

Please note that this test is only for the ZMPSTE24 gene.

For patients with suspected ZMPSTE24-related disorders, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References:**

- OMIM #600480: ZMPSTE24 gene
- OMIM #275210: Lethal Restricted Dermopathy
- OMIM #608612: MAD

**Genes**

ZMPSTE24

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of ZMPSTE24-Related disorders in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of ZMPSTE24-Related disorders in whom sequence analysis was negative.

**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) or ACD (yellow 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

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Sequence analysis of the ZMPSTE24 gene is available and is required before deletion/duplication analysis.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.