ZMPSTE24-related Disorders: ZMPSTE24 Gene Sequencing

Test Code: SZMPS
Turnaround time: 6 weeks
CPT Codes: 81479 x1

**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.

**References:**

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

**Genes**

**ZMPSTE24**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of ZMPSTE24-Related Disorders.
- Carrier testing in adults with a family history of ZMPSTE24-Related Disorders.

**Methodology**

PCR amplification of 10 exons contained in the ZMPSTE24 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**Detection**

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**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.

**Related Tests**

- Deletion/duplication analysis of the ZMPSTE24 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- 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.
- Sequencing and deletion/duplication analysis is available for the LMNA gene.