

Restrictive Dermopathy and Mandibuloacral Dysplasia Testing via *ZMPSTE24* Exon Sequencing (Test #400)

Brief Description: Restrictive Dermopathy (RD) (OMIM 275210) (also called tight skin contracture syndrome) is a rare disorder observed in newborns and characterized by tight, translucent and rigid skin, distinctive craniofacial abnormalities especially including mouth in the “O” position and micrognathia, and joint contractures. Live newborns with RD nearly always die within the first week of life. Mandibuloacral Dysplasia (MAD) (OMIM 248370 and 608612) is also rare and is characterized by mandibular and clavicular hypoplasia, joint contractures and lipodystrophy.

Genetics: Both RD and MAD are inherited in an autosomal recessive manner. Both disorders may be caused by mutations in either the *LMNA* or *ZMPSTE24* genes (Agarwal et al. Hum Mol Genet 12:1995-2001, 2003; Moulson et al. J Invest Dermatol 125:913-919, 2005; Navarro et al. Hum Mol Genet 14:1503-1513, 2005). Moulson et al. reported that all RD patients were either homozygous or compound heterozygous for causative *ZMPSTE24* mutations, as expected for a recessive disorder. For unknown reasons, Navarro et al. reported that all of their RD patients were heterozygous for causative mutations in this gene. A common deletion mutation spanning the entire gene is one possible explanation.

ZMPSTE24 is located at 1p34 and encodes a zinc metalloendoproteinase which is involved in processing of Lamin A (encoded by the *LMNA* gene). Causative mutations reported to date in *ZMPSTE24* have been frameshifts, missense and nonsense mutations, and one multi-exon deletion. PreventionGenetics also offers testing of the *LMNA* gene. It appears that at least for RD, *ZMPSTE24* carries more causative mutations than *LMNA* and should be sequenced first.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 10 coding exons of *ZMPSTE24* plus about 50 bp of flanking non-coding DNA on each side.

Indications for Test: Candidates for this test are patients with symptoms consistent with RD or MAD and family members of patients. We will sequence the *ZMPSTE24* gene in parents of affected children to determine which mutations they may carry. We will also sequence single or double exons in patients to confirm research results and in the family members of patients with known mutations to determine carrier status.

Sensitivity of Test: Literature results for these rare disorders are too limited to get precise estimates of sensitivity. Based on available information, we estimate that roughly 70% of RD patients and 20% of MAD patients will be found to carry two likely causative mutations in the *ZMPSTE24* sequencing test. Occasionally, only one mutation will be detected.

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

SPECIMEN REQUIREMENTS: See page 4 of the Requisition Form.

Price: Sequencing of *ZMPSTE24* Exons 1-10 **\$ 690**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification X10	83898	\$ 220	Sequencing X10	83904	\$ 310
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 50

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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