SMAD3 MUTATION ANALYSIS
JOHN WELSH CARDIOVASCULAR DIAGNOSTIC LABORATORY

SMAD3 gene encodes a protein that belongs to the SMAD family. SMAD proteins are signal transducers and transcriptional modulators that mediate multiple signaling pathways. This protein functions as a transcriptional modulator activated by transforming growth factor-beta (TGF-beta) and is thought to play a role in the regulation of carcinogenesis. SMAD3 binds the TRE element in the promoter region of many genes that are regulated by TGF-beta and, on formation of the SMAD3/SMAD4 complex, activates transcription. It also can form a SMAD3/SMAD4/JUN/FOS complex at the AP-1/SMAD site to regulate TGF-beta-mediated transcription. It has an inhibitory effect on wound healing probably by modulating both growth and migration of primary keratinocytes and by altering the TGF-mediated chemotaxis of monocytes. Human SMAD3 gene contains nine exons spanning 129 kb of genomic distance that was mapped to chromosome 15q22.33. Mutations in SMAD3 gene have been associated with patients of type I Loeys-Dietz syndrome, idiopathic pulmonary fibrosis, aneurysms-osteoarthritis syndrome (AOS) and colorectal cancer (CRC). Definitive genotype/phenotype correlations have not been described.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for SMAD3 mutations. Individuals are tested by DNA sequencing of the coding exons of the SMAD3 gene. We strongly recommend initial testing of a clearly affected individual, if available, in order to provide the greatest test sensitivity and clearest interpretation of results for subsequent family members. Genetic counseling is recommended for all individuals.

REASONS FOR REFERRAL

Molecular confirmation of type I Loeys-Dietz syndrome, idiopathic pulmonary fibrosis and aneurysms-osteoarthritis syndrome (AOS).

METHODOLOGY

Genomic DNA is analyzed for SMAD3 mutations by DNA sequencing of the coding exons of the SMAD3 gene, as well as the exon/intron junctions and a portion of the 5’ and 3’ untranslated region. Patient DNA is sequenced in both the forward and reverse orientations. If a mutation is identified, additional family members are analyzed only for the familial mutation by automatic fluorescent DNA sequencing.

SERVICE FEES

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<tr>
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<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
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<tr>
<td>Index Case (Male or Female)</td>
<td>$750 per sample</td>
<td>81405</td>
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<tr>
<td>Additional Family Members</td>
<td>$300 per sample; known familial mutation only</td>
<td>81403</td>
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SENSITIVITY

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-9 of SMAD3.

SPECIMEN REQUIREMENTS

Blood (preferred): EDTA (purple-top) tubes: Adult: 5 cc Child: 5 cc Infant: 2-3 cc
Tissue: Frozen (preferred), RNAlater
Other Body Fluids and Formalin-fixed, Paraffin-embedded Tissue: Call to inquire

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