SMAD4 MUTATION ANALYSIS

JOHN WELSH CARDIOVASCULAR DIAGNOSTIC LABORATORY

SMAD4 gene encodes a member of the SMAD family of signal transduction proteins which are phosphorylated and activated by transmembrane serine-threonine receptor kinases in response to TGF-beta signaling. SMAD4 forms homomeric complexes and heteromeric complexes with other activated SMAD proteins, which then accumulate in the nucleus and regulate the transcription of target genes. It binds to DNA and recognizes an 8-bp palindromic sequence (GTCTAGAC) called the SMAD-binding element (SBE). SMAD4 gene contains 11 exons spanning 55 kb of genomic distance that was mapped to chromosome 18q21.1. Multiple mutations in SMAD4 have been identified in patients with juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, aortopathy, primary pulmonary hypertension, Myhre syndrome, Peutz-Jeghers syndrome, prostate cancer, pancreatic cancer and colorctal cancer. SMAD4 mutations demonstrate autosomal dominant inheritance with a broad range of clinical severity both within and between families. Definitive genotype/phenotype correlations have not been described.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for SMAD4 mutations. Individuals are tested by DNA sequencing of the coding exons of the SMAD4 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 juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, aortopathy, primary pulmonary hypertension, Myhre syndrome, Peutz-Jeghers syndrome, prostate cancer, pancreatic cancer and colorctal cancer.

METHODOLOGY

Genomic DNA is analyzed for SMAD4 mutations by DNA sequencing of the coding exons of the SMAD4 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>
<th>Index Case (Male or Female)</th>
<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
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<td>$750 per sample</td>
<td>81406</td>
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<th>Additional Family Members</th>
<th>Direct and Institutional Billing</th>
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<tbody>
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<td>$300 per sample; known familial mutation only</td>
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SENSITIVITY


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