Activins are dimeric growth and differentiation factors that belong to the transforming growth factor-beta (TGF-beta) superfamily of structurally related signaling proteins. Activins signal through a heteromeric complex of receptor serine kinases, which include at least two type I (I and IB) and two type II (II and IIB) receptors. Type I receptors are essential for signaling; and type II receptors are required for binding ligands and for expression of type I receptors. Activin binds to type-2 receptor at the plasma membrane and activates its serine-threonine kinase. The activated receptor type-2 then phosphorylates and activates the type-1 receptor. Once activated, the type-1 receptor binds and phosphorylates the SMAD proteins SMAD2 and SMAD3, on serine residues of the C-terminal tail. Soon after their association with the activin receptor and subsequent phosphorylation, SMAD2 and SMAD3 are released into the cytoplasm where they interact with the common partner SMAD4. This SMAD complex translocates into the nucleus where it mediates activin-induced transcription. The ACVR2B gene encodes activin A type IIB receptor, which displays a 3- to 4-fold higher affinity for the ligand than activin A type II receptor. Diseases associated with ACVR2B include autosomal visceral heterotaxy and acvr2b-related visceral heterotaxy. Definitive genotype/phenotype correlations have not been described.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for ACVR2B mutations. Individuals are tested by automatic fluorescent DNA sequencing of the coding exons of the ACVR2B 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 the diagnosis of CHD, autosomal visceral heterotaxy and acvr2b-related visceral heterotaxy.

**METHODOLOGY**

Genomic DNA is analyzed for ACVR2B mutations by automatic fluorescent DNA sequencing of the coding exons of the ACVR2B 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>
<td>Additional Family Members</td>
<td>$300 per sample; Known familial mutation only</td>
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**SENSITIVITY**

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-11 of ACVR2B.

**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 or Formalin-fixed, Paraffin-embedded Tissue:** Call to inquire