NKX2.5, also known as human cardiac-specific homeobox (CSX), is a member of the NK2 class of homeodomain transcription factors. NKX2.5, composed of 2 exons and located at 5q34, encodes cardiac homeobox protein Nkx2.5, which is essential in cardiac development. Mutational analysis of NKX2.5 revealed three different heterozygous mutations predicted to disrupt the DNA-binding function of the homeodomain. Since the initial report, more than 30 mutations have been identified within NKX2.5. Heterozygous NKX2.5 mutations account for ~4% of all congenital heart disease (CHD) including atrial septal defect (ASD) with atrioventricular (AV) conduction defects, tetralogy of Fallot (TOF), heterotaxy, ventricular septal defect (VSD), and double-outlet right ventricle (DORV). Based on the analysis of phenotypes associated with NKX2.5 mutations, a genotype-phenotype correlation between AV block and specific types of NKX2.5 mutations has emerged. Frameshift or nonsense mutations at any location or homeodomain missense mutations are associated with an AV conduction block phenotype, whereas individuals with missense mutations in the amino or carboxy terminus do not show this phenotype. Mutations in NKX2.5 have been noted to demonstrate autosomal dominant inheritance with a variable clinical expression.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for NKX2.5 mutations. Individuals will be tested by automatic fluorescent DNA sequencing of all 2 exons of the NKX2.5 gene. Genetic counseling is recommended for all individuals in order to identify additional at-risk family members and to discuss reproductive issues.

**REASONS FOR REFERRAL**

- Molecular confirmation of the diagnosis of congenital heart disease (CHD) including atrial septal defect (ASD) with atrioventricular conduction defects, tetralogy of Fallot (TOF), heterotaxy, VSD, and DORV.

**METHODOLOGY**

Genomic DNA will be analyzed for NKX2.5 mutations by automatic fluorescent DNA sequencing of all 2 exons of the NKX2.5 gene, as well as the exon/intron junctions and a portion of the 5’ and 3’ untranslated regions. Patient DNA will be sequenced in both the forward and reverse orientations. If a mutation is identified, additional family members will be analyzed only for the familial mutation(s) by automatic fluorescent DNA sequencing.

**SERVICE FEES**

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<tr>
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<th>Direct and Institutional Billing</th>
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<td>Index Case (Full Gene)</td>
<td>$450 per sample</td>
<td>83891, 83898x2, 83904x4, 83912</td>
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<tr>
<td>Additional Family Members</td>
<td>$200 per sample; known familial mutation only</td>
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</tbody>
</table>

**SENSITIVITY**

DNA Sequencing Analysis: Approximately 99% detection of mutations in exons 1-2 of NKX2.5

**SPECIMEN REQUIREMENTS**

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

John Welsh Cardiovascular Diagnostic Laboratory • Section of Cardiology • Department of Pediatrics
Baylor College of Medicine • 1102 Bates Avenue, Suite 480.02 • Houston, TX 77030
PHONE: (832) 824-4155 • FAX: (832) 825-5159 • E-MAIL: yuxinf@bcm.edu
Web Site: [www.bcm.edu/pediatrics/welsh](http://www.bcm.edu/pediatrics/welsh)