Clinical Features:
Mutations in the NKX2.5 gene [OMIM #600584, 108900] have been described in numerous families with inherited forms of non-syndromic congenital heart disease (1-4). The most common phenotype associated with NKX2.5 mutations are atrial septal defect (ASD) and atrioventricular block (AVB). These abnormalities are highly penetrant, however some patients may have ASD or AVB alone. Many different forms of congenital heart disease can arise from NKX2.5 gene mutations including: ventral septal defect, tetralogy of fallot, hypoplastic left heart, pulmonic stenosis, anomalous pulmonary venous return, tricuspid valve abnormalities, Ebstein's anomaly, interrupted aortic arch, L-transposition of the great arteries, mitral valve abnormalities, coarctation of the aorta, and double outlet right ventricle. In addition, there are some forms of heart block that also arise from NKX2.5 gene mutations without additional congenital heart disease. Conduction system disease is often seen in individuals with NKX2.5 mutations. AVB is the most common manifestation, but the severity and age of onset differs among individuals and can be progressive with age (1, 4-6). Many patients require pacing devices and sudden deaths have occurred (1, 4, 5).

Inheritance:
Mutations in NKX2.5 cause autosomal dominant non-syndromic congenital heart disease. Recurrence risk for affected individuals and carrier parents is 50%. Not all family members with NKX2.5 mutations have cardiac defects, consistent with decreased penetrance [1-4]. Thus, individuals with isolated CHD and conduction system disease with or without family history should be considered for this analysis.

Molecular Genetics:
NKX2.5, a homeodomain-containing transcription factor, is a vital component of the complex developmental pathways that lead to normal cardiac development in multiple species. NKX2.5-null Drosophila lack any heart formation (7) and NKX2.5-null mice are embryonic lethal with cardiac development arrested at the looped stage (8, 9). In humans the NKX2.5 gene is located on chromosome 5q35 and made up of two exons. Approximately 30 different NKX2.5 mutations have been reported in familial and sporadic cases (1-6, 10-14). Missense, nonsense, frameshift, and splice site mutations have all been detected and many of them occur within the homeodomain [1].

Additional Resources:
American Heart Association
7272 Greenville Avenue
Dallas TX 75231
Phone: 800-242-8721
Congenital Heart Defects in Children

Congenital Heart Information Network (CHIN)
1561 Clark Drive
Yardley PA 19067
Phone: 215-493-3068
Email: mb@tchin.org
http://www.tchin.org/

Test methods:
We offer full gene sequencing of both coding exons and intron/exon boundaries. Deletion/duplication analysis of the NKX2.5 genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.
Patients with negative or unknown results can enroll in Dr. Elizabeth McNally’s research study at the University of Chicago for further studies.

**NKX2.5 sequencing analysis**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $430
- CPT codes: 81404
- Turn-around time: 4 weeks

**NKX2.5 deletion/duplication analysis**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $1000
- CPT codes: 81403
- Turn-around time: 4 weeks

**Testing for a known mutation in additional family members**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $390
- CPT codes: 81403
- Turn-around time: 3-4 weeks

**Prenatal testing for a known mutation**
- Sample specifications: 2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
- Cost: $540
- CPT codes: 81403
- Turn-around time: 1-2 weeks

**Results:**
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

**References:**