

The University of Chicago Genetic Services Laboratories



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NKX2.5 Analysis for Non-Syndromic Congenital Heart Disease

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]. Many patients require pacing devices and sudden deaths have occurred [1].

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 [5] and *NKX2.5*-null mice are embryonic lethal with cardiac development arrested at the looped stage [6]. 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 [1-4]. 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. Patients with negative or unknown results can enroll in Dr. Elizabeth McNally's research study at the University of Chicago for further studies.

Mutation analysis (sequencing)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$430
CPT codes:	83891, 83898, 83904, 83894, 83912
Turn-around time:	4 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
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:	\$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
Turn-around time:	1-2 weeks

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

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References:

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2. Goldmuntz, E., E. Geiger, and D.W. Benson, *NKX2.5 mutations in patients with tetralogy of fallot*. Circulation, 2001. **104**(21): p. 2565-8.
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4. Benson, D.W., et al., *Mutations in the cardiac transcription factor NKX2.5 affect diverse cardiac developmental pathways*. J Clin Invest, 1999. **104**(11): p. 1567-73.
5. Bodmer, R., *The gene tinman is required for specification of the heart and visceral muscles in Drosophila*. Development, 1993. **118**(3): p. 719-29.
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