The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu dnatesting.uchicago.edu
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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, 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 NKK2.5-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 to10 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 to10 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 to10 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:

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3. McElhinney DB, Geiger E, Blinder J et al. NKX2.5 mutations in patients with congenital heart disease. J Am Coll Cardiol 2003: 42: 1650-1655.
4. Schott JJ, Benson DW, Basson CT et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. Science 1998: 281: 108-111.
5. Gutierrez-Roelens I, Sluysmans T, Gewillig M et al. Progressive AV-block and anomalous venous return among cardiac anomalies associated with two novel missense mutations in the CSX/NKX2-5 gene. Hum Mutat 2002: 20: 75-76.
6. Hirayama-Yamada K, Kamisago M, Akimoto K et al. Phenotypes with GATA4 or NKX2.5 mutations in familial atrial septal defect. Am J Med Genet A 2005: 135: 47-52.
7. Bodmer R. The gene tinman is required for specification of the heart and visceral muscles in Drosophila. Development 1993: 118: 719-729.
8. Tanaka M, Chen Z, Bartunkova S et al. The cardiac homeobox gene Csx/Nkx2.5 lies genetically upstream of multiple genes essential for heart development. Development 1999: 126: 1269-1280.
9. Lyons I, Parsons LM, Hartley L et al. Myogenic and morphogenetic defects in the heart tubes of murine embryos lacking the homeo box gene Nkx2-5. Genes Dev 1995: 9: 1654-1666.
10. Watanabe Y, Benson DW, Yano S et al. Two novel frameshift mutations in NKX2.5 result in novel features including visceral inversus and sinus venosus type ASD. J Med Genet 2002: 39: 807-811.
11. Elliott DA, Kirk EP, Yeoh T et al. Cardiac homeobox gene NKX2-5 mutations and congenital heart disease: associations with atrial septal defect and hypoplastic left heart syndrome. J Am Coll Cardiol 2003: 41: 2072-2076.
12. Hosoda T, Komuro I, Shiojima I et al. Familial atrial septal defect and atrioventricular conduction disturbance associated with a point mutation in the cardiac homeobox gene CSX/NKX2-5 in a Japanese patient. Jpn Circ J 1999: 63: 425-426.
13. Ikeda Y, Hiroi Y, Hosoda T et al. Novel point mutation in the cardiac transcription factor CSX/NKX2.5 associated with congenital heart disease. Circ J 2002: 66: 561-563.
14. Kasahara H, Benson DW. Biochemical analyses of eight NKX2.5 homeodomain missense mutations causing atrioventricular block and cardiac anomalies. Cardiovasc Res 2004: 64: 40-51.