Gene Section
Mini Review

NKX2-5 (NK2 transcription factor related, locus 5 (Drosophila)).

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Identity

Other names: CSX; CSX1; NKX2E; Hs.54473; NM_004387; cardiac-specific homeobox
HGNC (Hugo): NKX2-5
Location: 5q35.2
Local order: cen---BNIP1---NKX2-5---STC2---tel.

DNA/RNA

Description
The gene has two exons and one intron.

Transcription
Transcription takes place in a telomere --> centromere orientation. The length of the processed mRNA is about 1500 bp.

Protein

Description
324 amino acids; 35-38 kDa, depending on phosphorylation status; contains one TN domain (residues 10-21), one homeodomain (residues 138-197), and one NK2 domain (residues 212-234).

Expression
Expression is mainly restricted to the heart. But during embryogenesis NKX2-5 expression has also been detected in spleen-precursor cells.

Localisation
Cytoplasmatic and nuclear, probably depending on phosphorylation status.

Pseudogene
Not known.

The gene for NKX2-5 comprizes two exons of 510 and 1075 bp, respectively. The length of the intron is 1540 bp. Positions of start and stop codons are indicated. These data refer to ENSEMBL transcript.
**Function**
Involved in differentiation processes in heart development and in homeostasis and survival of cardiac myocytes.

**Homology**
Homeodomain protein with membership of the NK2 / NKX family.

**Mutations**

**Note**
Among vertebrates, NKX2-5 is the most highly conserved of the Drosophila tinman homologs and subject to transcriptional control via complex series of cis-regulatory elements both proximal and distal of the transcription unit.

**Germinal**
Haploinsufficiency due to loss-of-function mutations is associated with atrioventricular conduction defects and tetralogy of Fallot.

**Somatic**
Recently identified in cardiac disease.

**Implicated in**

*t(5;14)(q35;q32) in acute lymphoblastic leukaemia (ALL) and t(5;14)(q35;q11) in chronic lymphocytic leukaemia*

**Note**
NKX2-5 lies circa 2 Mbp telomeric of TLX3 which is recurrently targeted for juxtaposition with BCL11B by t(5;14)(q35;q32) in a subset of patients (both pediatric and adult) in T-cell ALL. Studies performed on pediatric T-ALL cell lines have shown that visually identical t(5;14) rearrangements may target NKX2-5 or TLX3. Initial data suggest that the t(5;14) variant targeting NKX2-5 is clinically rare. The clinical involvement t(5;14)/NKX2-5 has only been recently identified but has yet to be published. In addition to T-ALL, NKX2-5 rearrangement has been reported in a case of chronic lymphocytic leukaemia (CLL) with t(14;11)(q35;q11) where the activating partner at 14q11 is TCRA/TCRD.

**Prognosis**
Unknown.

**Cytogenetics**
The t(5;14) rearrangements respectively targeting NKX2-5 and TLX3 which lies about 2Mbp centromeric are cytogenetically indistinguishable in both conventionally banded and chromosome painting preparations. In addition, both sets of rearrangements are cryptic as equal and similarly banded material from chromosomes 5 and 14 are exchanged. Thus, analysis using sets of BAC clones covering both TLX3 and NKX2-5 loci is necessary to distinguish these rearrangements.

**Hybrid/Mutated gene**
No.

Figure shows FISH analysis of t(5;14) in the pediatric T-ALL cell line PEER using three RP11 library clones located immediately centromeric (779o18, labelled red), spanning (466h21, green) and telomeric (45g21, yellow) of NKX2-5. (See below for map.) The rearrangement may be a simple insertion or, a double translocation whereby chromosome 14 material is first translocated onto the der(5) and then returned by a non-reciprocal copying process to the der(14) accompanied by genomic material surrounding NKX2-5.

Figure shows mutations causing various cardiac anomalies. NKX2-5 contains two exons encoding a 324-amino acid protein including a tinman domain (TN), homeodomain (black) and an NK2 domain. Truncation mutations are shown above, missense mutations below. Δ indicates deletion of the intron 1 splice donor site. Note clustering of mutations within the homeobox itself.
Abnormal protein
No

Oncogenesis
NKX2-5 is developmentally silenced in thymocytes. Formation of t(5;14) juxtaposes NKX2-5 with enhancer elements probably cognate with T-cell specific DNaseI hypersensitive sites present in the downstream regulatory region of BCL11B which plays a central role in thymic maturation. It is believed that both TLX3 and NKX2-5 are reactivated by similar mechanisms involving juxtaposition with T-cell specific regulatory regions. Structural similarities shared by NKX2-5, TLX1 and TLX3 add weight to this hypothesis.

Breakpoints

![Breakpoint Diagram]

Figure shows breakpoints described in ALL cell lines with t(5;14)(q35.2;q32) which juxtaposes NKX2-5 with the downstream region of BCL11B - outer breakpoints; and in a case of CLL with t(5;14)(q35.2;q11) where the activating locus was TRD - middle breakpoint. Completion of sequencing data at the NKX2-5 locus has repositioned some of the BAC clones, allowing further refinement of the breakpoint assignments. It is now clear that known breakpoints tightly flank NKX2-5 without disrupting the transcription unit itself. Thus, NKX2-5 translocations may also involve disruption of cis-regulatory elements as has been shown for TLX1 (HOX11) in t(10;14)(q24;q11) in T-ALL.

References

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