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Gene Section
Short Communication

STAG2 (Stromal Antigen 2)

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Abstract

Review on STAG2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: SA-2, SA2, SCC3B, bA517O1.1

HGNC (Hugo): STAG2

Location: Xq25

DNA/RNA

Description

The STAG2 gene consists of 35 exons spanning 142 Kbp, located at chromosome Xq25.

Transcription

Transcription takes place in a centromere --> telomere orientation (plus strand). Transcription of STAG2 gene generates 19 different mRNA transcripts, the longest is 6045 bp containing 34 exons (ENST00000371160).
There are multiple transcription factor binding sites (TFBS) for GATA3 present in the regulatory first intron of STAG2 summarized above (Fig. 1).

Pseudogene

There are no known pseudogenes.

Protein

Description

The STAG2 gene encodes two alternative isoforms:
- A: Q8N3U4-1, 1231 aa, 141.3 KDa
- B: Q8N3U4-2, 1268 aa, 145.7 KDa

Expression

STAG2 mRNA is expressed in cells from most tissues. Peak expression occurs in T-cell and early erythroid compartments, and in the uterus.

Figure 1. Clustering of GATA3 TFBS in STAG2 regulatory region. Schema showing multiple GATA3 TFBS present in the regulatory intron of STAG2. For additional TFBS see: SABiosciences.

Protein Sequence (Q8N3U4) from UniProt (Isoform A 1231 AA).

MIAAPEIPTDFNLLQESETHFSSDTDFEDIEGKNQKQGKGKTCKKGKKGPAEKGKGGNGGGKPPSGPNRMNGHHQQNGVENMLFEVVK
MGKSAMQSVVDDWIESYKHDRDIALLDLINFFIQCSGCKGVVTAEMFRHMQNSEIIRKMTEEFDEDSGDYPLTMAGPQWKKFKSSFCEFI
GVLVRQCQYSIIYDEYMMDTVISLLTGLSDSQVRAFRHTSTLAAMKLMTALVNVALNLSINMDNTQRQYEAERNKMIGKRANERELLLQK
RKELQENQDEIENMMNAIFKGVFVHRYRDAIAEIRAICIEEIGIWMKMYSDAFLNDSYLKYVGWTMHDKQGEVRLKCLTALQGLYYNKEL
NSKLELFTSRFKDRIVSMTLDKEYDVAVQAIKLLTLVLQSSEEVLTAEDCENVYHLVYSAHRPVAVAAGEFLYKKLFSRRDPEEDGMMRRGRQ
GPNANLVKTLVFFFLESELHEHAAYLVDSMWDCATELLKDWECMNSLLLEEPLSGEEALTDRQESALIEIMLCTIRQAAECHPPVGRGTGKR
VLTAKEKKTQLDDRTKITELFAVALPQLLAKYSVDAEKVTNLLQLPQYFDLEIYTTGRLEKHLDALLRQIRNIVEKHTDTDVLEACSKTYHALCN
EEFTIFNRVDISRSQLIDELADKFNRLLEDFLQEGEEPDEDDAYQVLSTLKRITAFHNAHDLSKWDLFACNYKLLKTGIENGDMPEQIVIHALQ
CTHYVILWQLAKITESSSTKEDLLRLKKQMRVFCQICQHYLTNVNTTVKEQAFTILCDILMIFSHQIMSGGRDMLEPLVYTPDSSLQSELLSFIL
DHVFIEQDDDNNSADGQQEDEASKIEALHKRRNLLAAFCKLIVYTVVEMNTAADIFKQYMKYYNDYGDIIKETMSKTRQIDKIQCAKTLILS
LQQLFNEMIQENGYNFDRSSSTFSGIKELARRFALTFGLDQLKTREAIAMLHKDGIEFAFKEPNPQGESHPPLNLAFLDILSEFSSKLLRQDKR
TVYVYLEKFMTFQMSLRREDVWLPLMSYRNSLLAGGDDDTMSVISGISSRGSTVRSKKSKPSTGKRKVVEGMQLSLTEESSSSDMWLSRE
QTLHTPVMMQTPQLTSTIMREPKRLRPEDSFMSVYPMQTEHHQTPLDYNRRGTSLMEDDEEPIVEDVMMSSEGRIEDLNEGMDFDTM
DIDLPPSKNRRERTELKPDFFDPASIMDESVLGVSMF

Figure 2. Domain structure of STAG2 and amino acid sequence.

Lowest expression is found in brain, heart, liver, lung and testis. STAG2 is also overexpressed in T-/B-cell acute lymphoblastic leukemia (ALL) and in other hematopoietic neoplasias, followed by small cell lung cancer, neuroblastoma and medulloblastoma.

It has been reported that the expression of STAG2 protein is lost in some cancer types such as glioblastoma, Ewing's sarcoma, and melanoma (Solomon et al., 2011), colorectal carcinomas, gastric carcinomas and prostate carcinomas (Kim et al., 2012).

Localisation

Nucleus albeit reportedly with transmembrane potential.

Function

STAG2 forms the cohesin complex together with SMC1, SMC3, and SCC1. The cohesin complex is a ring-like structure and is required for cohesion of sister chromatids after DNA replication.

The complex is cleaved at the metaphase-anaphase transition and dissociates from chromatin for separation of sister chromatids (Xiao et al., 2011). While STAG2 mediates centromere cohesion, that of telomeres is mediated by the homologous STAG1 (Canudas et al., 2009; Remeseiro et al., 2012).

Cohesin also plays a major part in the organization of interphase chromatin, including the orchestration of gene expression in relation to cell cycle where STAG2 also plays a key role along with the universal transcriptional repressor CCCTC-binding factor (CTCF). CTCF-cohesin interactions require contact between STAG2 and C-terminal CTCF which facilitate recruitment of other cohesion complex proteins and formation of the cohesion ring. This interaction is also needed for CTCF to function as a transcriptional insulator.

Homology

Two paralogs are known: STAG1 and STAG3 which can replace STAG2 in the cohesion complex.

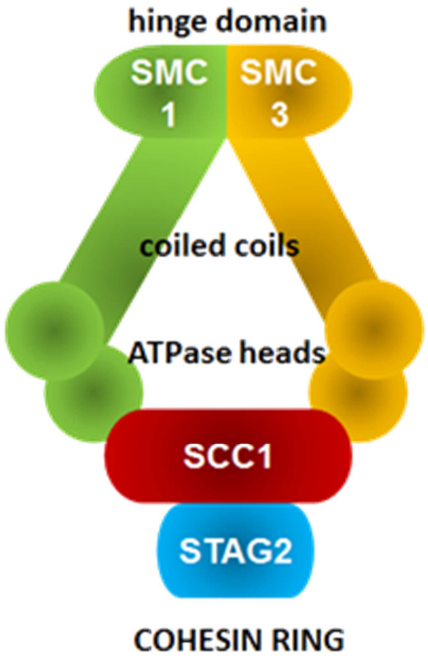

Figure 3. Cohesin complex showing ring structure. Diagram showing ring structure of cohesin complex (modified from Hagstrom and Meyer, 2003, and Remeseiro and Losada, 2013).

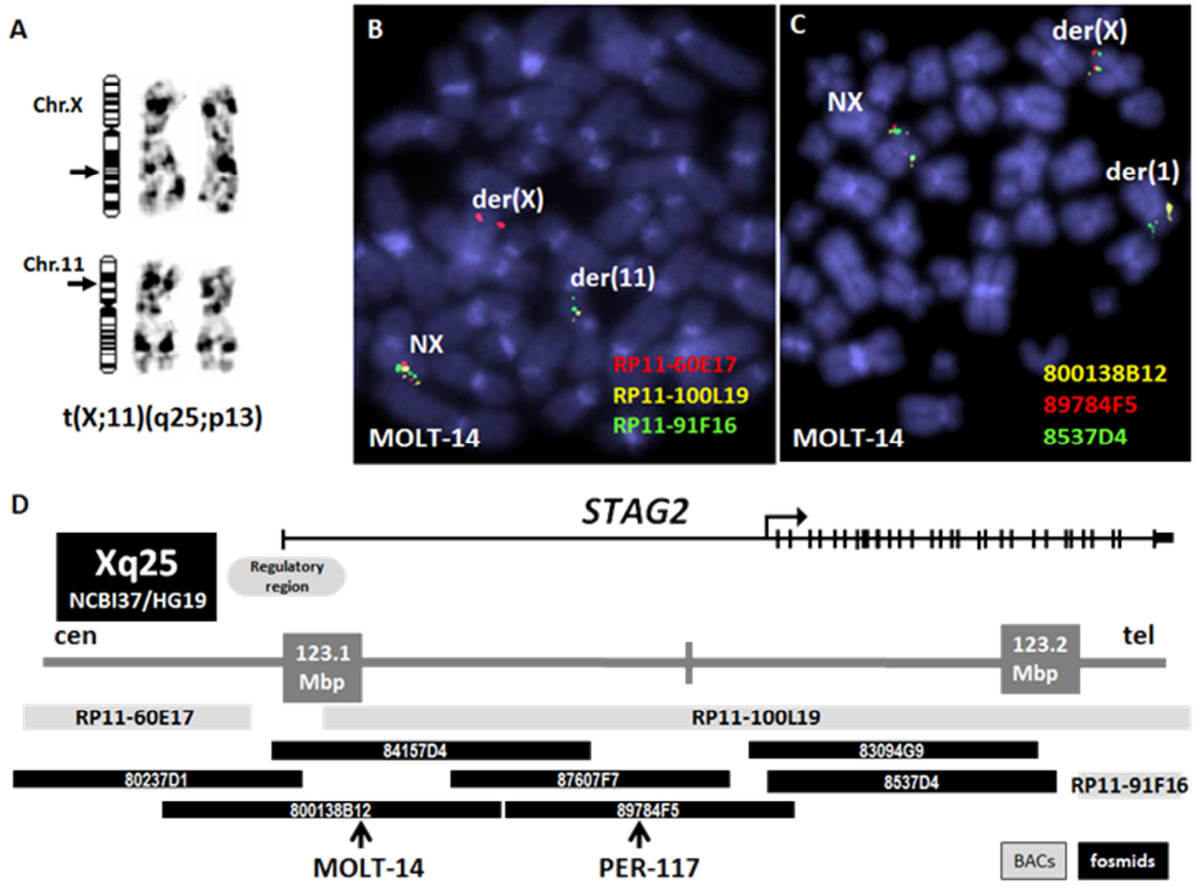

Figure 4. Cytogenetic analysis of t(X;11) effecting juxtaposition of STAG2 and LMO2. Image shows FISH analysis of t(X;11)(q25;p13) in a T-ALL cell line (DSM ACC 437). Note that this translocation is cryptic in G-banding (Fig. A). FISH using BAC and fosmid clones (Fig. B, C) places breakpoints in MOLT-14 and another T-ALL cell line PER-117, both inside the first (regulatory) intron of STAG2. In both cell lines expression of STAG2 is lost, attributable to divestment of this region which includes a deeply conserved cluster of regulatory motifs, including transcription factor binding sites and DNaseI sensitive sites. Upregulation of LMO2 in both cell lines occurred, concomitant with acquisition of the upstream STAG2 region. Fig. D: Genomic map of Xq25 showing breakpoints in regulatory region in relation to clones used for FISH. Figure redrawn and updated from Chen et al. (2011).

Mutations

Recurrent STAG2 gene mutations were reported in glioblastoma, melanoma and Ewing's sarcoma (Solomon et al., 2011). Recently, STAG2 gene was found frequently mutated in myeloid neoplasms, including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), chronic myelogenous leukemia (CML) and classical myeloproliferative neoplasms (MPN) (Kon et al., 2013). Other studies observed lower frequencies of STAG2 mutation (Chung et al., 2012; Kim et al., 2012).It remains unclear whether mutations affecting STAG2 operate to induce aneuploidy (Solomon et al., 2011; Kolodner et al., 2011), or simply to abrogate expression (Rocquain et al., 2010; Kon et al., 2013).

Implicated in

Myeloid neoplasms

Note

Mutation and deletion of the STAG2 gene was identified in 5.8% (13/224) of MDS, 10.2% (9/88) of CMML, 6.4% (10/157) of AML, 3.1% (2/64) of CML, and 1.3% (1/77) of MPN: the STAG2 alterations were mostly exclusive with alterations involving other components of cohesin complex (SMC1, SMC3, and RAD21) and were significantly associated with mutations in TET2, ASXL1, and EZH2 (Kon et al., 2013).

t(X;11)(q25;p13)

Disease

T-ALL: only two T-ALL cell lines described so far.

Cytogenetics

t(X;11)(q25;p13) in MOLT-14 cells and t(X;1;11)(q25;p13;p13) in PER-117 cells. The rearrangement is fully cryptic (see below).

Oncogenesis

t(X;11)(q25;p13) results in simultaneous upregulation of LMO2 and silencing of STAG2 by juxtaposition of the far upstream region of LMO2 with the first regulatory intron of STAG2 (Chen et al., 2011).

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