Atlas of Genetics and Cytogenetics in Oncology and Haematology

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# Gene Section
## Mini Review

# KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog)

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Published in Atlas Database: June 2000

Online updated version : http://AtlasGeneticsOncology.org/Genes/KITID127.html
DOI: 10.4267/2042/37632



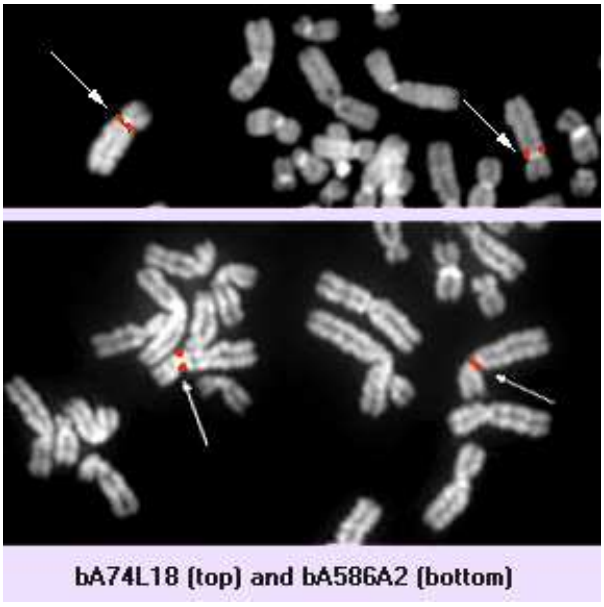
## Identity

**Other names:** SCFR (Stem Cell Factor Receptor); CD117

**HGNC (Hugo):** KIT

**Location:** 4q12

**Local order:** centromere-PDGFRA-KIT-KDR-telomere.




KIT (4q12) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

## DNA/RNA

### Description

Spans 89 kb; 21 exons; size of intron 1: 37,4 kb.

### Transcription

5,23 kb mRNA; alternative splicing of exon 9 gives rise to two isoforms, KitA and Kit, that differ by the presence or absence of four aminoacids.

## Protein

### Description

976 aa; 145 kDa; type III receptor tyrosine kinase; contains an extracellular domains with 5 Ig-like loops, a highly hydrophobic transmenbrane domain (23 aa), and an intracellular domain with tyrosine kinase activity split by a kinase insert (KI) in an ATP-binding region and in the phosphotransferase domain.

### Expression

Hematopoietic stem cells, mast cells, melanocytes, germ-cell lineages and ICCs (Interstitial cells of Cajal).

### Localisation

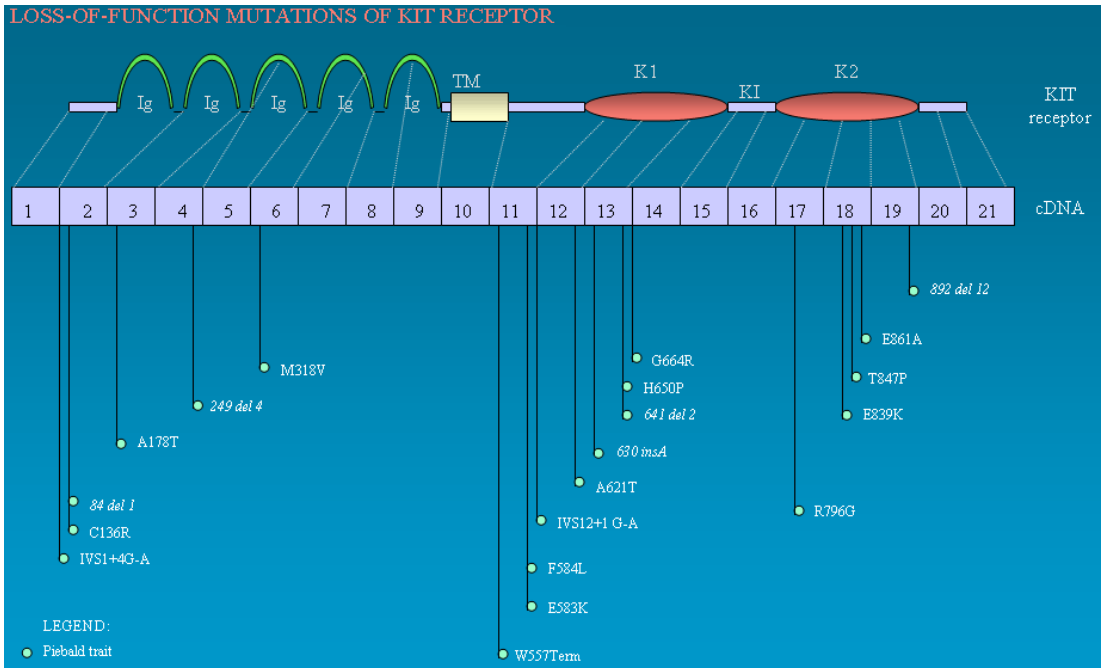
Plasma membrane.

### Function

SCF/MGF receptor with tyrosine kinase activity; binding of ligand (SCF) induces receptor dimerization, autophosphorylation and signal transduction via molecules containing SH2- domains.

### Homology

With CSF-1R, PDGFRb, PDGFRa, and FLT3.




# Mutations

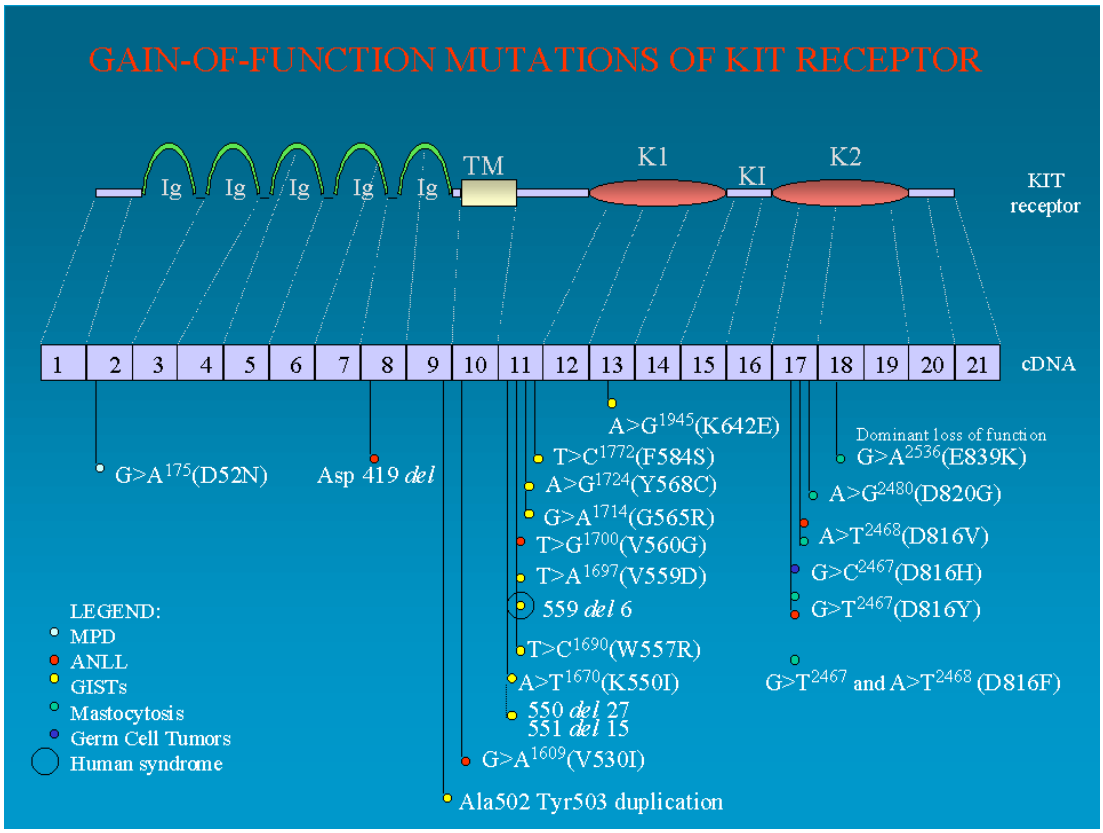
**Note:** See diagrams: Loss-of-function mutations, and Gain-of-function mutations.

## *Germinal*

In piebaldism, and in familial gastrointestinal stromal tumours (see below).

## *Somatic*

In aggressive mastocytosis, mast cell leukemia, ANLL with/without mast cell involvement, myeloproliferative disorders, colon carcinoma and gastrointestinal stromal tumours and germ cell tumors (GCCs).



# Implicated in

## *Piebaldism*

**Disease**

Autosomal dominant disorder of pigmentation; loss of function abnormalities of the c-kit gene have been demonstrated in 59% of the typical patients.

## *Familial gastrointestinal stromal tumours and sporadic gastrointestinal stromal tumours (GISTs)*

**Disease**

GISTs are the most common mesenchymal tumors in the human digestive tract; they originate from kit-expressing cells (ICCs), and often have activating c-kit mutations clustered in the juxtamembrane domain.

## *Systemic mast cell disease (SMCD)*

**Disease**

Mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, gastrointestinal tract and skin; gain of function mutations are detected in most patients.

**Prognosis**

Depending on the four clinical entities recognized: indolent form, form associated with hematologic disorder, aggressive SMCD and mast cell leukemia; leukemic transformation with mast cell involvement is characterized by rapid progression of disease with a survival time less than 1 year.

**Oncogenesis**

Clinical features of malignant hematopoietic cell growth are influenced by the time, the location of c-kit mutative events, and the number of associated lesions.

## *Core binding factor leukemias (ANLL-M2 with t(8;21) (link), (ANLL-M4Eo with inv(16))*

**Disease**

Characterized by disruption and loss of CBFa2/AML1 - CBFb/PEBP2b function.

Myelomonoblastic leukemia cells are marked by combined positivity for the stem cell antigens CD34, CD117 and high frequency of c-kit mutations (see Figure on CBF leukemia and KIT mutations).

# To be noted

**Note**

Loss of expression of c-KIT appears to be associated with progression of some tumors (melanoma) and autocrine/paracrine stimulation of the c-kit/SCF system may participate in human solid tumors such as lung, breast, testicular and gynecological malignancies.

# References

Vandenbark GR, deCastro CM, Taylor H, Dew-Knight S, Kaufman RE. Cloning and structural analysis of the human c-kit gene. Oncogene. 1992 Jul;7(7):1259-66

Ezoe K, Holmes SA, Ho L, Bennett CP, Bolognia JL, Brueton L, Burn J, Falabella R, Gatto EM, Ishii N. Novel mutations and deletions of the KIT (steel factor receptor) gene in human piebaldism. Am J Hum Genet. 1995 Jan;56(1):58-66

Longley BJ, Tyrrell L, Lu SZ, Ma YS, Langley K, Ding TG, Duffy T, Jacobs P, Tang LH, Modlin I. Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. Nat Genet. 1996 Mar;12(3):312-4

Andre C, Hampe A, Lachaume P, Martin E, Wang XP, Manus V, Hu WX, Galibert F. Sequence analysis of two genomic regions containing the KIT and the FMS receptor tyrosine kinase genes. Genomics. 1997 Jan 15;39(2):216-26

Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998 Jan 23;279(5350):577-80

Gari M, Goodeve A, Wilson G, Winship P, Langabeer S, Linch D, Vandenberghe E, Peake I, Reilly J. c-kit proto-oncogene exon 8 in-frame deletion plus insertion mutations in acute myeloid leukaemia. Br J Haematol. 1999 Jun;105(4):894-900

Longley BJ Jr, Metcalfe DD, Tharp M, Wang X, Tyrrell L, Lu SZ, Heitjan D, Ma Y. Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. Proc Natl Acad Sci U S A. 1999 Feb 16;96(4):1609-14

Sakurai S, Fukasawa T, Chong JM, Tanaka A, Fukayama M. C-kit gene abnormalities in gastrointestinal stromal tumors (tumors of interstitial cells of Cajal. Jpn J Cancer Res. 1999 Dec;90(12):1321-8

Tian Q, Frierson HF Jr, Krystal GW, Moskaluk CA. Activating c-kit gene mutations in human germ cell tumors. Am J Pathol. 1999 Jun;154(6):1643-7

Beghini A, Peterlongo P, Ripamonti CB, Larizza L, Cairoli R, Morra E, Mecucci C. C-kit mutations in core binding factor leukemias. Blood. 2000 Jan 15;95(2):726-7

Lux ML, Rubin BP, Biase TL, Chen CJ, Maclure T, Demetri G, Xiao S, Singer S, Fletcher CD, Fletcher JA. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. Am J Pathol. 2000 Mar;156(3):791-5

*This article should be referenced as such:*

Larizza L, Beghini A. KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog). Atlas Genet Cytogenet Oncol Haematol. 2000; 4(3):96-98.