

## Gene Section

### Short Communication

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

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## Abstract

Review on KIT, with data on DNA, on the protein encoded, and where the gene is implicated.

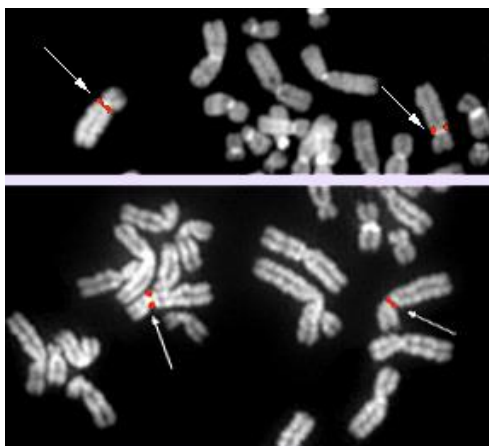
## Identity

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

**HGNC (Hugo):** KIT

**Location:** 4q12

**Local order:** centromere-PDGFR A -KIT-KDR-telomere.



bA74L18 (top) and bA586A2 (bottom)

KIT (4q12) - Courtesy Mariano Rocchi

## DNA/RNA

### Description

The KIT gene located on human chromosome 4q11 and contains 21 exons. Exon1 encodes the initiation codon, exon 2-9 encodes the extracellular domain, exon 10 the transmembrane region and exons 11-21 the intracellular part.

### Transcription

The 5.23 kb mRNA is alternatively spliced into two isoforms differing in the presence or absence of exon 9. This splicing gives rise to KIT variants that differ by the presence or absence of the amino acid sequence GNNK (denoted KIT and KITA, respectively). In addition there is alternative splicing occurring in humans, but not in mice, giving rise of isoforms that differ by the presence or absence of a serine residue in the kinase insert region. In postmeiotic germ cells a shorter KIT transcript is expressed that gives rise to a truncated version of KIT (tr-KIT) containing part of the kinase domain and the C-terminal tail.

## Protein

### Description

976 aa; 145 kDa; type III receptor tyrosine kinase; glycoprotein; contains an extracellular domains with 5 Ig-like loops, a highly hydrophobic

transmembrane 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. Tr-KIT does not contain the whole kinase domain and is therefore kinase inactive.

### Expression

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

Expression pattern in the mouse suggest that KIT may play a role in tissues such as nervous system, placenta, heart, lung and midgestational kidneys.

### Localisation

Plasma membrane.

The truncated tr-KIT lacks the transmembrane domain and is hence not present at the plasma membrane.

### Function

KIT is a cell surface receptor with tyrosine kinase activity; binding of ligand KITLG (also denoted MGF or SCF) induces receptor dimerization, autophosphorylation and signal transduction via molecules containing SH2- domains. KIT signaling leads to cell proliferation, survival, migration and differentiation.

### Homology

with CSF-1R, PDGFRB, PDGFRA, and FLT3.

## Mutations

### Note

See figures Loss-of-function mutations and Gain-of-function mutations.

## Implicated in

### Piebaldism

#### Disease

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

### Familial Gastrointestinal Stromal Tumors and sporadic gastrointestinal stromal tumors (GISTs)

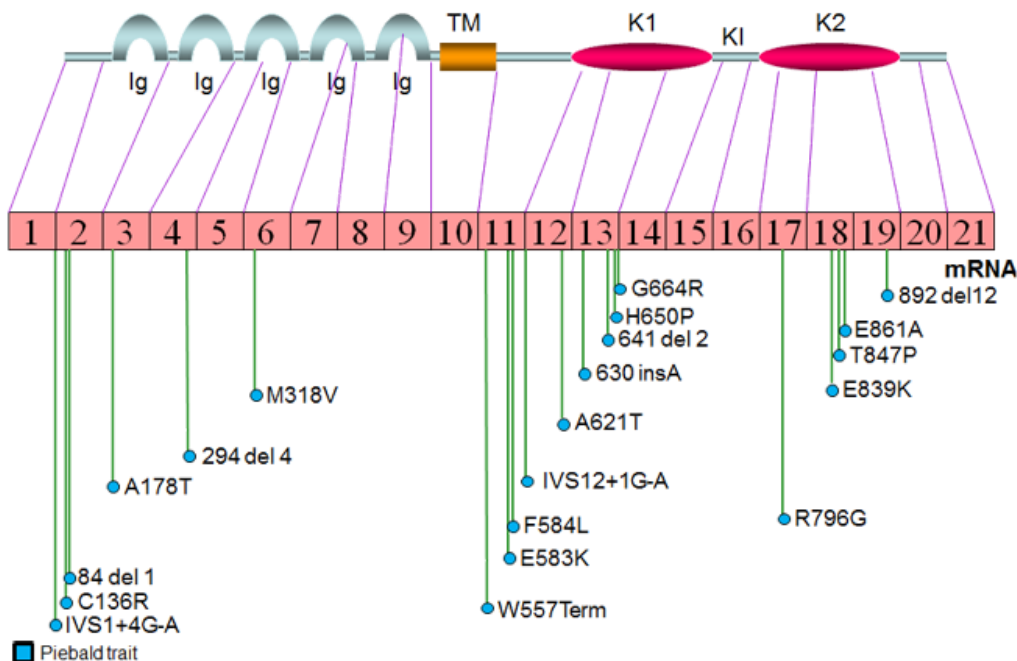
#### Disease

GISTs are the most common mesenchymal tumors in the human digestive tract; they originate from KIT-expressing cells (ICCs).

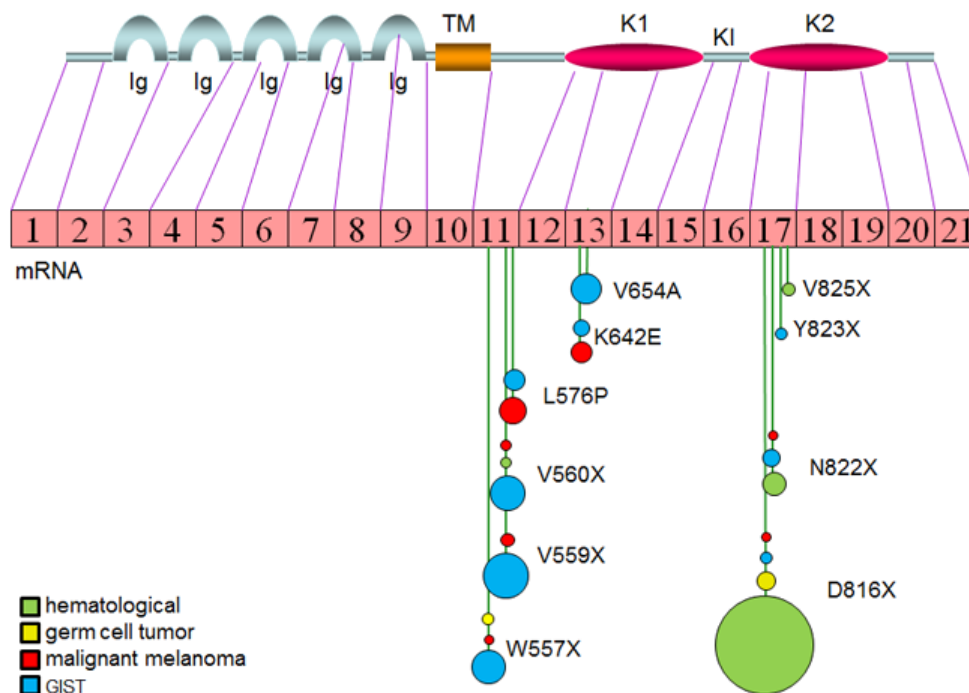
All GISTs express KIT which is frequently (80-85% of the cases) mutated in exon 11 encoding the juxtamembrane domain.

However, also mutations in exon 9 (encoding the extracellular region) and 17 (encoding a region around the activation loop in the kinase domain) have been found.

Most GIST cells produce SCF thus establishing autocrine stimulation.



Loss-of-function mutations.



Gain-of-function mutations.

## 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.

About 90% of patients with systemic mastocytosis have mutation in exon 17 in KIT, often Asp-816 is replaced with Val.

In children with systemic mastocytosis the frequency of KIT mutations in exon 17 is lower (about 40%), but mutations in other KIT regions are found in 40% of the children, for example mutation in exon 8 and 9 (encoding Ig-like domain 5 in the extracellular region of KIT).

### Prognosis

The prognosis depends 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.

## Small Cell Lung cancer (SCLC)

### Disease

KIT overexpression is found in 70% of SCLC

patients. Co-expression of KIT and SCF has been found to create an autocrine loop. The prognostic value of KIT expression is not clear.

## Testicular Carcinoma

### Disease

Activating mutations in KIT exon 17 is found in about 25% of seminomas. Often Asp-816 is replaced with a Val or His residue.

## Melanoma

### Disease

KIT is important for the development of melanocytes. The about 80% of melanomas contain BRAF mutations, but a subset contain activating KIT mutations. Interestingly in acral melanomas (affecting foot soles or palms) there is a higher frequency of tumors with activating KIT mutations (20-25% of cases). Examples of KIT mutations found in melanoma are L576P (in exon 11) and K642E (in exon 13). Mutation in position 816 (in exon 17) has also been observed but is not so frequent occurring.

## Acute Myeloid Leukemia

### Disease

KIT expression can be found in about 85% of AML cells. KIT activation can occur by different mechanisms: 1) co-expression of SCF causing an autocrine loop 2) activating mutations in exon 17 affecting Asp-816 or Asn-822. Interestingly, KIT mutations occurs primarily in a subset of leukemias containing inv(16) or t(8;21), so-called core factor binding AML. Apart from exon 17 mutations, also

internal tandem duplications in exon 11 have been described.

### Prognosis

Presence of D816V mutation in KIT is a poor prognostic factor.

## To be noted

### Note

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

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