

## Gene Section

### Review

# ERBB2 (erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian))

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## Identity

**Other names:** v-erb-b2; HER2; NEU; TKR1; NGL; Her-2/neu; C-erbB-2

**HGNC (Hugo):** ERBB2

**Location:** 17q11.2-q12



Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

### Note

Tyrosine-kinase receptor (RTK). The HER family of RTKs consists of four receptors: epidermal growth factor receptor (EGFR, also called HER-1 or erbB-1), HER-2 (also called erbB-2 or Neu), HER-3 and HER-4 (also called erbB-3 and erbB-4, respectively).

## DNA/RNA

### Description

Sequence length 30528; CDS 3768. 27 exons; total exon length 4477, max. exon length 969, min exon length 48. Number of SNPs 11. Polymorphisms: allelic variations at amino acid positions 654 and 655 of isoform (a) (positions 624 and 625 of isoform (b)) have

been reported, with the most common Allele B1 (Ile-654/Ile-655); allele B2 (Ile-654/Val-655); allele B3 (Val-654/Val-655). This nucleotide polymorphism could be associated with development of gastric carcinoma and with breast cancer risk, particularly among younger women.

### Transcription

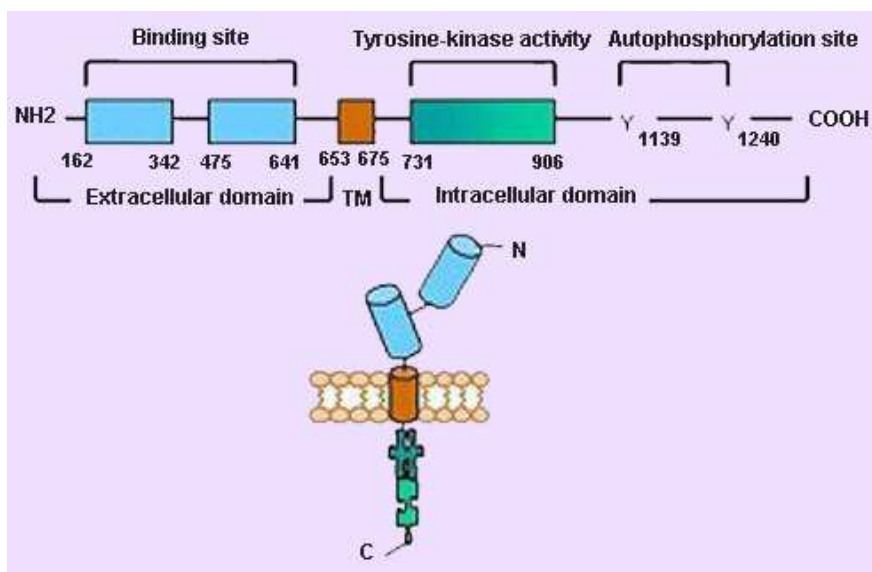
Alternative splicing results in several additional transcript variants, some encoding different isoforms and others that have not been fully characterized.

**mRNA Transcript Variant:** This variant (1) represents the shorter transcript but encodes the longer isoform (a) (protein: erbB-2 isoform (a)).

**mRNA Transcript Variant:** This variant (2) (protein: erbB-2 isoform (b)) contains additional exons at its 5' end and lacks an alternate 5' noncoding exon, compared to variant (1). These differences result in translation initiation at an in-frame, downstream AUG and an isoform (b) with a shorter N-terminus compared to isoform (a).

**mRNA Transcript Variant:** herstatin HER2-ECD 1300 bp alternative erbB-2 transcript that retains intron 8. This alternative transcript specifies 340 residues identical to subdomains I and II from the extracellular domain of p185erbB-2 followed by a unique C-terminal sequence of 79 aa encoded by intron 8. The herstatin mRNA is expressed in normal human fetal kidney and liver, but is at reduced levels relative to p185erbB-2 mRNA in carcinoma cells that contain an amplified erbB-2 gene.

**mRNA Transcript Variant:** An alternative transcript form of the human homologous gene



**HER2 protein: schematic representation**

Receptor tyrosin-kinases (RTKs) are cell surface allosteric enzymes consisting of:

- an extracellular ligand-binding domain (blue)
- a single transmembrane (TM) domain has an extensive homology to the epidermal growth factor receptor (brown)
- a cytoplasmic domain with catalytic activity (green).

erbB-2, containing an in-frame deletion encompassing exon 19, has been detected in human breast carcinomas.

## Protein

### Description

erbB2 encodes an 185-kDa, 1255 amino acids, orphan receptor tyrosine kinase, it displays potent oncogenic activity when overexpressed. The protooncogene consists of three domains: a single transmembrane domain that separates an intracellular kinase domain from an extracellular ligand-binding domain.

### Expression

HER2 protein is expressed in several human organs and tissues: normal epithelium, endometrium and ovarian epithelium and at neuromuscular level; prostate, pancreas, lung, kidney, liver, heart, hematopoietic cells. HER2 expression is low in mononuclear cells from bone marrow, peripheral blood (PB) and mobilized PB. The higher expression has been found in cord blood-derived cells. Quiescent CD34+ progenitor cells from all blood sources and resting lymphocytes are HER2 negative, but the expression of this receptor is up-regulated during cell-cycle recruitment of progenitor cells. Similarly, it increases in mature, hematopoietic proliferating cells, underlying the correlation between HER2 and the proliferating status of hematopoietic cells.

### Localisation

Plasma membrane.

### Function

#### ACTIVATION AND INTERACTIONS:

For the other member of the HER family, ligand binding induces receptor homo- or heterodimerization, which is essential for TKs activation and subsequent recruitment of target proteins, in turns initiating a complex signaling cascade that leads into distinct transcriptional programs. There are several HER-specific ligands. HER2, which apparently has no direct or specific ligand, plays a major coordinating role in the HER network because of its ability to enhance and stabilize the dimerization: each receptor with a specific ligand appears in fact to prefer HER-2 as its heterodimeric partner. HER-2-containing heterodimers are characterized by extremely high signaling potency because HER-2 dramatically reduces the rate of ligand dissociation, allowing strong and prolonged activation of downstream signalling pathways.

#### SIGNALING AND CELLULAR:

The most important intracellular pathways activated by HER2 are those involving mitogen activated protein kinase and phosphatidylinositol-3 kinase. HER2 expression in cancer, besides its role in proliferation, enhances and prolongs those survival signals, associating up-regulation of this receptor to the malignant phenotype. At the same time, and depending on cellular status, the role of this receptor in controlling cell fate can also lead to differentiation and apoptosis.

#### PHYSIOLOGICAL:

Role in development and differentiation:

HER2 has several non-oncogenic roles in regulating growth, differentiation, apoptosis and/or remodeling in

normal mammary glands. Dominant-negative forms of HER2 have significant defects in mammary development and lactation.

HER2 has an important role in development and function of heart. Cre-Lox technology to mutate erbB-2 specifically in ventricular cardiomyocytes leads to a severe cardiomyopathy. This is inferred also by the adverse cardiac side effects observed in breast cancer patients treated with the monoclonal anti-HER2 Ab Trastuzumab.

HER2 has a role in control of Schwann cell myelination and it has been demonstrated that HER2 signaling is also critical for oligodendrocyte differentiation in vivo.

HER2 has a dual role in both muscle spindle maintenance and survival of myoblasts. Muscle-specific HER2 KO results in fact in viable mice with a progressive defect in proprioception due to loss of muscles spindles.

### **Homology**

Homolog to Avian erythroblastic leukemia viral (v-erb-b) oncogen 2.

## **Mutations**

### **Somatic**

The Cancer Genome Project and Collaborative Group sequenced the erbB-2 gene from 120 primary lung tumors and identified 4% that had mutations within the kinase domain; in the adenocarcinoma subtype of lung cancer, 10% of cases had mutations.

In non small cell lung cancer (adenocarcinoma) the following erbB-2 mutations were found: insertion/duplication of GCATACGTGATG at nucleotide 2322 of the erbB-2 gene, resulting in a 4-amino acid insertion (AYVM) at codon 774. insertion of CTGTGGGCT at nucleotide 2335 of the erbB-2 gene, resulting in a 3-amino acid insertion (VGS) starting at codon 779; a 2-bp substitution in the erbB-2 gene, TT-CC at nucleotides 2263 and 2264, resulting in a leu755-to-pro (L755P) substitution. In a glioblastoma a 2740G-A transition in the erbB-2 gene that caused a glu914-to-lys substitution (E914K).

In a gastric tumor a 2326G-A transition in the erbB-2 gene that caused a gly776-to-ser (G776S) substitution. In an ovarian tumor, a 2570A-G transition in the erbB-2 gene that caused an asn857-to-ser (N857S) substitution.

## **Implicated in**

### **Hematological malignancies**

#### **Disease**

HER2 expression can be detected in blast cells from patients with hematological malignancies including

acute lymphoblastic leukemia (ALL). It could be used as a potential target for the application of HER2-directed treatment strategies in ALL including vaccination approaches.

### **Bladder cancer**

#### **Prognosis**

HER2 is overexpressed in 25% to 40% of several human tumors and associated with the malignancy of the disease, high mitotic index and a shorter survival time for the patient. Overexpression of ErbB-2 is associated with transitional cell carcinoma of the bladder. HER2 overexpression occurs in muscle-invasive urothelial carcinomas of the bladder and is associated with worse survival; amplifications of erbB-2 gene are also frequently linked to alterations of the TOP2A gene in bladder cancer.

### **Breast carcinoma**

#### **Prognosis**

HER-2 overexpression, occurring in 25-30% of human breast cancers, is associated to shorter time to relapse and lower overall survival. Overexpression of the erbB-2 gene, is associated with tumor aggressiveness, and with patient responsiveness to doxorubicin, cyclophosphamide, methotrexate, fluorouracil (CMF), and to paclitaxel, whereas tamoxifen was found to be ineffective and even detrimental in patients with HER2-positive tumors. In Paget's disease of breast, HER2 protein overexpression is caused by amplification of the erbB-2 gene. HER2 has a role in this disease of the breast, where the epidermis of the nipple is infiltrated by large neoplastic cells of glandular origin. It seems that binding of heregulin-alfa to the receptor complex on Paget cells results in chemotaxis of these breast cancer cells.

### **Cervical cancer**

#### **Prognosis**

HER2 may be activated in the early stage of pathogenesis of cervical carcinoma in geriatric patients and is frequently amplified in squamous cell carcinoma of the uterine cervix.

### **Childhood Medulloblastoma**

#### **Prognosis**

Overexpression of HER2 in medulloblastoma is associated with poor prognosis and metastasis and HER2-HER4 receptor heterodimerization is of particular biological significance in this disease.

### **Colorectal cancer**

#### **Prognosis**

Overexpression of HER2 occurs in a significant number of colorectal cancers. It was significantly associated with poor survival and related to tumor progression in colorectal cancer.

## **Oral squamous cell carcinoma**

### **Prognosis**

E6/E7 proteins of HPV type 16 and HER2 cooperate to induce neoplastic transformation of primary normal oral epithelial cells. Overexpression of HER2 receptor is a frequent event in oral squamous cell carcinoma and is correlated with poor survival.

## **Gastric cancer**

### **Prognosis**

HER2 amplification/overexpression does not seem to play a role in the molecular pathogenesis of most gastrinomas. However, mild gene amplification occurs in a subset of them, and overexpression of this receptor is associated with aggressiveness of the disease. HER2 is correlated with tumor histological differentiation and is associated with poor prognosis in well-differentiated gastric adenocarcinoma.

## **Germ-cell testicular tumor**

### **Prognosis**

A significant correlation was observed between HER2 overexpression and clinical outcome in germ-cell testicular tumors.

## **Cholangiocarcinoma**

### **Prognosis**

Increased HER2 expression contributes to the development of cholangiocarcinogenesis into an advanced stage associated with tumor metastasis. In addition, overexpression of HER2 and COX-2 correlated directly with tumor differentiation.

## **Lung cancer**

### **Prognosis**

HER2 is overexpressed in less than 20% of patients with non-small cell lung cancer (NSCLC) and studies have shown that overexpression of this receptor is correlated with a poor prognosis in both resected and advanced NSCLC.

## **Osteosarcoma**

### **Prognosis**

Higher frequency of HER2 expression has been observed in samples from patients with metastatic disease at presentation and at the time of relapse, and it correlates with worse histologic response and decreased event-free survival.

## **Ovarian cancer**

### **Prognosis**

Patients with HER2-overexpression have a significantly worse prognosis compared to patients with HER2-negative tumors.

## **Pancreatic adenocarcinoma**

### **Prognosis**

Overexpression of HER-2 in pancreatic adenocarcinoma seems to be a result of increased transcription rather than gene amplification. The coexpression of HER2 oncogene protein, epidermal growth factor receptor, and TGF-beta1 in pancreatic ductal adenocarcinoma is related to the histopathological grades and clinical stages of tumors.

## **Primary Fallopian tube carcinoma**

### **Prognosis**

This disease is a rare form of female cancer where the HER2 overexpression plays a role in tumorigenesis.

## **Prostate cancer**

### **Prognosis**

The expression of ERBB2 in prostate cancer is relatively low, but is up-modulated at onset of hormone resistance.

## **Salivary gland tumor**

### **Prognosis**

Several results demonstrated significant positive staining of HER2 in the salivary tumorigenic tissue but not in the surrounding non-tumorigenic tissue, pointing to a biological role in the tumorigenic process.

## **Synovial sarcoma**

### **Prognosis**

The presence of increased levels of HER2 in synovial sarcoma is associated with a more favorable clinical course.

## **To be noted**

### **Note**

Possible therapeutic strategies: 1) growth inhibitory antibodies (like Trastuzumab), used alone or in combination with standard chemotherapeutics; 2) tyrosin kinase inhibitors (TKI); 3) active immunotherapy, because the HER2 oncoprotein is immunogenic in some breast carcinoma patients.

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