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Gene Section

Review

ERBB2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian))

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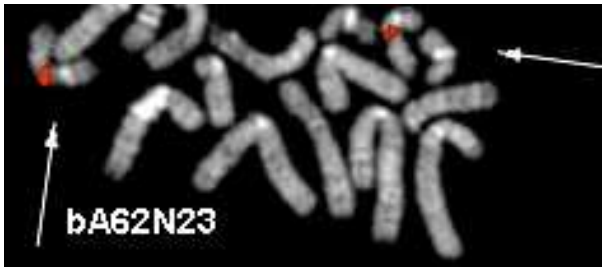
Identity

Other names: CD340; HER2; HER-2; HER-2/neu; MLN 19; NEU; NGL; TKR1

Location: 17q12



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: 40522; CDS: 3678. 30 exons, 26 coding exons; total exon length: 4816, max exon length: 969, min exon length: 48. Number of SNPs: 17.

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 erbB-2, containing an in-frame deletion encompassing exon 19, has been detected in human breast carcinomas.
- **mRNA transcript variant:** an alternative transcript form of the human homologous gene erbB-2, called HER2Δ16, has been detected in human breast carcinomas. This splicing variant, contains an in-frame deletion and encodes a receptor lacking exon 16, which immediately precedes the transmembrane domain containing two cysteines. The loss of these cysteine residues might induce a change in the conformation of HER2 receptor extracellular domain that promotes intermolecular disulfide bonding and, in turn, homodimers capable of transforming cells. Ectopic expression of HER2Δ16 promotes receptor dimerization, cell invasion, and trastuzumab resistant tumor cell lines. The potential metastatic and oncogenic properties of HER2Δ16 were mediated through direct coupling of HER2Δ16 to Src kinase.

Protein

Description

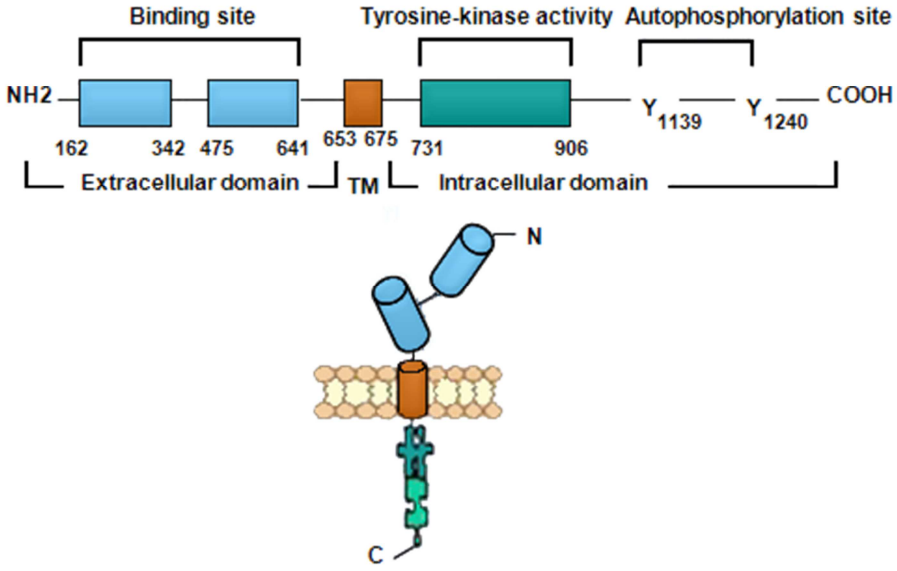
erbB2 encodes a 185-kDa, 1255 amino acids, orphan receptor tyrosine kinase, and displays potent oncogenic activity when overexpressed. The proto-oncogene consists of three domains: a single transmembrane domain that separates an intracellular kinase domain from an extracellular ligand-binding domain. An aberrant form of HER2, missing the extracellular domain, so-called
HER2p95, has been found in some breast cancers. HER2p95 is constitutively active because the external domain of these receptors acts as an inhibitor until they are bound by ligand. This isoform can cause resistance to trastuzumab, an antibody that works by binding to a domain in the external domain of HER2. HER2p95 fragments arise through at least 2 different mechanisms: proteolytic shedding of the extracellular domain of the full-length receptor and translation of the mRNA encoding HER2 from internal initiation codons. Shedding of the ectodomain of HER2 generates a 95- to 100-kDa HER2 p95 membrane-anchored fragment. Translation of the mRNA encoding HER2 can be initiated from the AUG codon that gives rise to the full-length protein of 1255 amino acids or, alternatively, from 2 internal initiation codons at positions 611 and 678, located upstream and downstream of the transmembrane domain, respectively.

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.



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 grow factor receptor (brown); a cytoplasmic domain with catalityc activity (green).

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 turn 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 signaling pathways.

Signaling and cellular

The most important intracellular pathways activated by HER2 are those involving mitogen activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K). HER2 expression in cancer, besides its role in proliferation, enhances and prolongs survivals 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 lung cancer a C44645G transition in the erbB-2 gene that caused a pro1170-to-ala substitution (P1170A).

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 also 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. Furthermore, HER2 overexpression and amplification in urothelial carcinoma of the bladder is found associated with MYC co-amplification.

Breast carcinoma

Prognosis

Normal tissues have a low content of HER2 membrane protein. Overexpression of HER2 is seen in 20% of breast and it confers worse biological behavior and clinical aggressiveness in breast cancer. Breast cancers can have up to 25 to 50 copies of the HER2 gene and up to a 40- to 100-fold increase in HER2 protein resulting in 2 million receptors expressed at the tumor cell surface. The differential HER2 expression between normal tissues and tumors helps to define HER2 as an ideal treatment target. Trastuzumab, the first treatment targeting HER2, is well tolerated in patients and has little toxicity because its effects are relatively specific for cancer cells overexpressing HER2. HER2 amplification is a relatively early event in human breast tumorigenesis, occurring in almost 50% of in situ carcinomas. HER2 status is maintained during progression to invasive disease and to nodal and distant metastasis. The fact that only 20% of invasive breast cancers are HER2 amplified suggests that many HER2-amplified in situ cancers never progress to the invasive stage. HER2 amplification defines a subtype of breast cancer with a unique signature of genes and this is maintained during progression. Some tumors lose HER2 expression following treatment with trastuzumab, presumably by selection of a HER2-negative clone not killed by treatment. Conversely, HER2 may become positive in some initially negative tumors over time, especially after endocrine therapy targeting ER. Indeed, estrogen receptor has been shown to downregulate HER2 and, conversely, HER2 is able to downregulate ER expression. Therefore, it is not surprising that blocking ER might upregulate HER2 and that blocking HER2 might upregulate ER. HER2-amplified breast cancers have unique biological and clinical characteristics. They have increased sensitivity to certain cytotoxic agents such as doxorubicin, relative resistance to hormonal agents, and propensity to metastasize to the brain and viscera. HER2-amplified tumors have an increased sensitivity to doxorubicin possibly due to coamplification of the topoisomerase-2 gene, which is near the HER2 locus on chromosome 17 and is the target of the drug. Half of HER2-positive breast cancers are ER positive but they generally have lower ER levels, and many have p53 alterations. These tumors have higher proliferation rates and more aneuploidy and are associated with poorer patient prognosis. The poor outcome is dramatically improved with appropriate chemotherapy combined with the HER2-targeting drug trastuzumab. 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-alpha to the receptor complex on Paget cells results in chemotaxis of these breast cancer cells. The isoforms HER2p95 and HER2Δ16 are found in some breast cancers and the expression of these hyperactive forms of HER2 may contribute to the malignant progression.

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 overexpression in patients with gastric cancer, and it has been solidly correlated to poor outcomes and a more aggressive disease. The overall HER2 positive rate is about 22%. HER2 overexpression rate in gastric cancer varies according to the site of the tumor. A higher overexpression rate (36%) was shown in gastroesophageal junction (GEJ) tumors in comparison to 21% in gastric tumors.

Germ-cell testicular tumor

Prognosis

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

Cholangiocarcinoma

Prognosis

Data are still controversial about HER2 role in this carcinoma. 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. However, other studies report that HER2 expression is associated with more favorable clinical features, such as a polypoid macroscopic type and absence of other organ involvement, and has been reported that the proportion of HER2-positive cases in papillary adenocarcinoma is higher than in other histological types and is associated with an early disease stage. HER2 is preferentially expressed in well differentiated component, and it is also expressed in dedifferentiated components in progressive cases.

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. HER2 overexpression has an important function in the biology of NSCLC and may have a prognostic value for patients with metastatic 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. HER2 could be an effective target for the immunotherapy of osteosarcoma, especially the type with high metastatic potential.

Ovarian cancer

Prognosis

HER2 overexpression varies from 9% to 32% of all cases of ovarian cancer and its overexpression is more frequent in advanced stage of ovarian cancer. Overexpression of HER2 in ovarian cancer cells leads to faster cell growth, higher abilities in DNA repair and colony formation. A cross-talk between HER2 and estrogen receptor (ER) was identified in ovarian cancer cells. Estrogen has been proven to induce the phosphorylation of HER2, and initiate the HER2's signaling pathway.

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. The blockade of HER2 inhibits the growth of pancreatic cancer cells in vitro. HER2 overexpression was reported to accumulate in well differentiated pancreas adenocarcinomas whereas it is only infrequently found in poorly differentiated or undifferentiated tumors, in vivo and in vitro analyses have suggested that targeting HER2 might increase treatment effects of conventional chemotherapies of pancreas adenocarcinoma. However, unlike in breast cancer, the application of antibodies directed against HER2 has not yet become an established therapy for pancreas adenocarcinoma.

Prostate cancer

Prognosis

HER2 plays pivotal roles in prostate cancer. Studies have shown that 25% of untreated primary tumors, 59% of localized tumors after neoadjuvant hormone therapy, and 78% of metastatic tumors overexpressed HER2. Several lines of evidence have implicated HER2 as a key mediator in the recurrence of prostate cancer to a hormone-refractory, androgen-independent tumor, which is the hallmark of prostate cancer progress. The driving force for prostate cancer recurrence is the reactivation of androgen receptor (AR), which is a type of nuclear receptors, activated by steroid hormone but ablated in hormonal therapy. Phosphorylation and reactivation of AR stimulate cancer cell growth and trigger tumor progression. It has been observed that overexpression of HER2 kinase enhanced AR function and hormone-independent growth in prostate tumor cells. HER2 activated AR through the MAPK pathway. Additionally, the HER2/HER3 dimmer increases AR protein stability and promotes the binding of AR to the promoter region of its target genes, resulting in AR activation in an androgen-depleted environment.

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. HER2 amplification is present predominantly in tumors with high HER2 expression and seems to be the dominant mechanism for HER2 overexpression in this tumor type.

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 HER2 oncoprotein is immunogenic in some breast carcinoma patients; 4) dimerization inhibitor antibodies, like Pertuzumab: its binding to HER2 inhibits the dimerization of HER2 with other HER receptors.

References

Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177-82

Di Fiore PP, Segatto O, Taylor WG, Aaronson SA, Pierce JH. EGF receptor and erbB-2 tyrosine kinase domains confer cell specificity for mitogenic signaling. Science. 1990 Apr 6;248(4951):79-83

Papewalis J, Nikitin AYu, Rajewsky MF. G to A polymorphism at amino acid codon 655 of the human erbB-2/HER2 gene. Nucleic Acids Res. 1991 Oct 11;19(19):5452

Tateishi M, Toda T, Minamisono Y, Nagasaki S. Clinicopathological significance of c-erbB-2 protein expression in human gastric carcinoma. J Surg Oncol. 1992 Apr;49(4):209-12

Kolodziejczyk P, Yao T, Oya M, Nakamura S, Utsunomiya T, Ishikawa T, Tsuneyoshi M. Long-term follow-up study of patients with gastric adenomas with malignant transformation. An immunohistochemical and histochemical analysis. Cancer. 1994 Dec 1;74(11):2896-907

Mitra AB, Murty VV, Pratap M, Sodhani P, Chaganti RS. ERBB2 (HER2/neu) oncogene is frequently amplified in squamous cell carcinoma of the uterine cervix. Cancer Res. 1994 Feb 1;54(3):637-9

Motojima K, Furui J, Kohara N, Izawa K, Kanematsu T, Shiku H. erbB-2 expression in well-differentiated adenocarcinoma of the stomach predicts shorter survival after curative resection. Surgery. 1994 Mar;115(3):349-54

Beerli RR, Graus-Porta D, Woods-Cook K, Chen X, Yarden Y, Hynes NE. Neu differentiation factor activation of ErbB-3 and ErbB-4 is cell specific and displays a differential requirement for ErbB-2. Mol Cell Biol. 1995 Dec;15(12):6496-505

Bühring HJ, Sures I, Jallal B, Weiss FU, Busch FW, Ludwig WD, Handgretinger R, Waller HD, Ullrich A. The receptor tyrosine kinase p185HER2 is expressed on a subset of B-lymphoid blasts from patients with acute lymphoblastic leukemia and chronic myelogenous leukemia. Blood. 1995 Sep 1;86(5):1916-23

Gilbertson RJ, Pearson AD, Perry RH, Jaros E, Kelly PJ. Prognostic significance of the c-erbB-2 oncogene product in childhood medulloblastoma. Br J Cancer. 1995 Mar;71(3):473-7

Horan T, Wen J, Arakawa T, Liu N, Brankow D, Hu S, Ratzkin B, Philo JS. Binding of Neu differentiation factor with the extracellular domain of Her2 and Her3. J Biol Chem. 1995 Oct 13;270(41):24604-8

Lee KF, Simon H, Chen H, Bates B, Hung MC, Hauser C. Requirement for neuregulin receptor erbB2 in neural and cardiac development. Nature. 1995 Nov 23;378(6555):394-8

Carlomagno C, Perrone F, Gallo C, De Laurentiis M, Lauria R, Morabito A, Pettinato G, Panico L, D'Antonio A, Bianco AR, De Placido S. c-erb B2 overexpression decreases the benefit of adjuvant tamoxifen in early-stage breast cancer without axillary lymph node metastases. J Clin Oncol. 1996 Oct;14(10):2702-8

Tzahar E, Waterman H, Chen X, Levkowitz G, Karunagaran D, Lavi S, Ratzkin BJ, Yarden Y. A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. Mol Cell Biol. 1996 Oct;16(10):5276-87

Gilbertson RJ, Perry RH, Kelly PJ, Pearson AD, Lunec J. Prognostic significance of HER2 and HER4 coexpression in childhood medulloblastoma. Cancer Res. 1997 Aug 1;57(15):3272-80

Graus-Porta D, Beerli RR, Daly JM, Hynes NE. ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. EMBO J. 1997 Apr 1;16(7):1647-55

Xia W, Lau YK, Zhang HZ, Liu AR, Li L, Kiyokawa N, Clayman GL, Katz RL, Hung MC. Strong correlation between c-erbB-2 overexpression and overall survival of patients with oral squamous cell carcinoma. Clin Cancer Res. 1997 Jan;3(1):3-9

Giani C, Casalini P, Pupa SM, De Vecchi R, Ardini E, Colnaghi MI, Giordano A, Ménard S. Increased expression of c-erbB-2 in hormone-dependent breast cancer cells inhibits cell growth and induces differentiation. Oncogene. 1998 Jul 30;17(4):425-32

Kwong KY, Hung MC. A novel splice variant of HER2 with increased transformation activity. Mol Carcinog. 1998 Oct;23(2):62-8

Olayioye MA, Graus-Porta D, Beerli RR, Rohrer J, Gay B, Hynes NE. ErbB-1 and ErbB-2 acquire distinct signaling properties dependent upon their dimerization partner. Mol Cell Biol. 1998 Sep;18(9):5042-51

Balsari A, Casalini P, Tagliabue E, Greco M, Pilotti S, Agresti R, Giovanazzi R, Alasio L, Rumio C, Cascinelli N, Colnaghi MI, Ménard S. Fluctuation of HER2 expression in breast carcinomas during the menstrual cycle. Am J Pathol. 1999 Nov;155(5):1543-7

Doherty JK, Bond C, Jardim A, Adelman JP, Clinton GM. The HER-2/neu receptor tyrosine kinase gene encodes a secreted autoinhibitor. Proc Natl Acad Sci U S A. 1999 Sep 14;96(19):10869-74

Ménard S, Casalini P, Tomasic G, Pilotti S, Cascinelli N, Bufalino R, Perrone F, Longhi C, Rilke F, Colnaghi MI. Pathobiologic identification of two distinct breast carcinoma subsets with diverging clinical behaviors. Breast Cancer Res Treat. 1999 May;55(2):169-77

Nezu M, Sasaki H, Kuwahara Y, Ochiya T, Yamada Y, Sakamoto H, Tashiro H, Yamazaki M, Ikeuchi T, Saito Y, Terada M. Identification of a novel promoter and exons of the c-ERBB-2 gene. Biochem Biophys Res Commun. 1999 May 19;258(3):499-505

Rabczyński JK, Kochman AT. Primary cancer of the fallopian tube with transitional differentiation. Clinical and pathological assessment of 6 cases. Neoplasma. 1999;46(2):128-31

Chung TK, Cheung TH, To KF, Wong YF. Overexpression of p53 and HER-2/neu and c-myc in primary fallopian tube carcinoma. Gynecol Obstet Invest. 2000;49(1):47-51

Garratt AN, Voiculescu O, Topilko P, Charnay P, Birchmeier C. A dual role of erbB2 in myelination and in expansion of the schwann cell precursor pool. J Cell Biol. 2000 Mar 6;148(5):1035-46

Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. EMBO J. 2000 Jul 3;19(13):3159-67

Schelfhout VR, Coene ED, Delaey B, Thys S, Page DL, De Potter CR. Pathogenesis of Paget's disease: epidermal heregulin-alpha, motility factor, and the HER receptor family. J Natl Cancer Inst. 2000 Apr 19;92(8):622-8

Xie D, Shu XO, Deng Z, Wen WQ, Creek KE, Dai Q, Gao YT, Jin F, Zheng W. Population-based, case-control study of HER2 genetic polymorphism and breast cancer risk. J Natl Cancer Inst. 2000 Mar 1;92(5):412-7

Casalini P, Botta L, Menard S. Role of p53 in HER2-induced proliferation or apoptosis. J Biol Chem. 2001 Apr 13;276(15):12449-53

Kim YS, Konoplev SN, Montemurro F, Hoy E, Smith TL, Rondón G, Champlin RE, Sahin AA, Ueno NT. HER-2/neu overexpression as a poor prognostic factor for patients with metastatic breast cancer undergoing high-dose chemotherapy with autologous stem cell transplantation. Clin Cancer Res. 2001 Dec;7(12):4008-12

Ménard S, Valagussa P, Pilotti S, Gianni L, Biganzoli E, Boracchi P, Tomasic G, Casalini P, Marubini E, Colnaghi MI, Cascinelli N, Bonadonna G. Response to cyclophosphamide, methotrexate, and fluorouracil in lymph node-positive breast cancer according to HER2 overexpression and other tumor biologic variables. J Clin Oncol. 2001 Jan 15;19(2):329-35

Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol. 2001 Feb;2(2):127-37

Aishima SI, Taguchi KI, Sugimachi K, Shimada M, Sugimachi K, Tsuneyoshi M. c-erbB-2 and c-Met expression relates to cholangiocarcinogenesis and progression of intrahepatic cholangiocarcinoma. Histopathology. 2002 Mar;40(3):269-78

Andrechek ER, Hardy WR, Girgis-Gabardo AA, Perry RL, Butler R, Graham FL, Kahn RC, Rudnicki MA, Muller WJ. ErbB2 is required for muscle spindle and myoblast cell survival. Mol Cell Biol. 2002 Jul;22(13):4714-22

Endo K, Yoon BI, Pairojkul C, Demetris AJ, Sirica AE. ERBB-2 overexpression and cyclooxygenase-2 up-regulation in human cholangiocarcinoma and risk conditions. Hepatology. 2002 Aug;36(2):439-50

Gandour-Edwards R, Lara PN Jr, Folkins AK, LaSalle JM, Beckett L, Li Y, Meyers FJ, DeVere-White R. Does HER2/neu expression provide prognostic information in patients with advanced urothelial carcinoma? Cancer. 2002 Sep 1;95(5):1009-15

Goebel SU, Iwamoto M, Raffeld M, Gibril F, Hou W, Serrano J, Jensen RT. Her-2/neu expression and gene amplification in gastrinomas: correlations with tumor biology, growth, and aggressiveness. Cancer Res. 2002 Jul 1;62(13):3702-10

Hirsch FR, Varella-Garcia M, Franklin WA, Veve R, Chen L, Helfrich B, Zeng C, Baron A, Bunn PA Jr. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. Br J Cancer. 2002 May 6;86(9):1449-56

Huang YW, Li MD, Wu QL, Liu FY. [Expression and clinical significance of p53 and c-erbB2 in geriatric women with cervical carcinoma]. Ai Zheng. 2002 Mar;21(3):297-300

Khan AJ, King BL, Smith BD, Smith GL, DiGiovanna MP, Carter D, Haffty BG. Characterization of the HER-2/neu oncogene by immunohistochemical and fluorescence in situ hybridization analysis in oral and oropharyngeal squamous cell carcinoma. Clin Cancer Res. 2002 Feb;8(2):540-8

Knösel T, Yu Y, Stein U, Schwabe H, Schlüns K, Schlag PM, Dietel M, Petersen I. Overexpression of c-erbB-2 protein correlates with chromosomal gain at the c-erbB-2 locus and patient survival in advanced colorectal carcinomas. Clin Exp Metastasis. 2002;19(5):401-7

Ménard S, Balsari A, Casalini P, Tagliabue E, Campiglio M, Bufalino R, Cascinelli N. HER-2-positive breast carcinomas as a particular subset with peculiar clinical behaviors. Clin Cancer Res. 2002 Feb;8(2):520-5

Ozcelik C, Erdmann B, Pilz B, Wettschureck N, Britsch S, Hübner N, Chien KR, Birchmeier C, Garratt AN. Conditional mutation of the ErbB2 (HER2) receptor in cardiomyocytes leads to dilated cardiomyopathy. Proc Natl Acad Sci U S A. 2002 Jun 25;99(13):8880-5

Savinainen KJ, Saramäki OR, Linja MJ, Bratt O, Tammela TL, Isola JJ, Visakorpi T. Expression and gene copy number analysis of ERBB2 oncogene in prostate cancer. Am J Pathol. 2002 Jan;160(1):339-45

Zhang L, Yuan SZ. Expression of c-erbB-2 oncogene protein, epidermal growth factor receptor, and TGF-beta1 in human pancreatic ductal adenocarcinoma. Hepatobiliary Pancreat Dis Int. 2002 Nov;1(4):620-3

Delektorskaya VV, Perevoshchikov AG, Kushlinskii NE. Immunohistological study of NM 23 and C-erbB-2 expression in primary tumor and metastases of colorectal adenocarcinoma. Bull Exp Biol Med. 2003 May;135(5):489-94

Junttila TT, Laato M, Vahlberg T, Söderström KO, Visakorpi T, Isola J, Elenius K. Identification of patients with transitional cell carcinoma of the bladder overexpressing ErbB2, ErbB3, or specific ErbB4 isoforms: real-time reverse transcription-PCR analysis in estimation of ErbB receptor status from cancer patients. Clin Cancer Res. 2003 Nov 1;9(14):5346-57

Kim JY, Sun Q, Oglesbee M, Yoon SO. The role of ErbB2 signaling in the onset of terminal differentiation of oligodendrocytes in vivo. J Neurosci. 2003 Jul 2;23(13):5561-71

Kuraoka K, Matsumura S, Hamai Y, Nakachi K, Imai K, Matsusaki K, Oue N, Ito R, Nakayama H, Yasui W. A single nucleotide polymorphism in the transmembrane domain coding region of HER-2 is associated with development and malignant phenotype of gastric cancer. Int J Cancer. 2003 Nov 20;107(4):593-6

Latif Z, Watters AD, Dunn I, Grigor KM, Underwood MA, Bartlett JM. HER2/neu overexpression in the development of muscle-invasive transitional cell carcinoma of the bladder. Br J Cancer. 2003 Oct 6;89(7):1305-9

Moliterni A, Ménard S, Valagussa P, Biganzoli E, Boracchi P, Balsari A, Casalini P, Tomasic G, Marubini E, Pilotti S, Bonadonna G. HER2 overexpression and doxorubicin in adjuvant chemotherapy for resectable breast cancer. J Clin Oncol. 2003 Feb 1;21(3):458-62

Müller MR, Grünebach F, Kayser K, Vogel W, Nencioni A, Brugger W, Kanz L, Brossart P. Expression of her-2/neu on acute lymphoblastic leukemias: implications for the development of immunotherapeutic approaches. Clin Cancer Res. 2003 Aug 15;9(9):3448-53

Nagler RM, Kerner H, Ben-Eliezer S, Minkov I, Ben-Itzhak O. Prognostic role of apoptotic, Bcl-2, c-erbB-2 and p53 tumor markers in salivary gland malignancies. Oncology. 2003;64(4):389-98

Nakamura H, Saji H, Ogata A, Hosaka M, Hagiwara M, Kawasaki N, Kato H. Correlation between encoded protein

overexpression and copy number of the HER2 gene with survival in non-small cell lung cancer. Int J Cancer. 2003 Jan 1;103(1):61-6

Nuciforo PG, Pellegrini C, Fasani R, Maggioni M, Coggi G, Parafioriti A, Bosari S. Molecular and immunohistochemical analysis of HER2/neu oncogene in synovial sarcoma. Hum Pathol. 2003 Jul;34(7):639-45

Simon R, Atefy R, Wagner U, Forster T, Fijan A, Bruderer J, Wilber K, Mihatsch MJ, Gasser T, Sauter G. HER-2 and TOP2A coamplification in urinary bladder cancer. Int J Cancer. 2003 Dec 10;107(5):764-72

Tan D, Deeb G, Wang J, Slocum HK, Winston J, Wiseman S, Beck A, Sait S, Anderson T, Nwogu C, Ramnath N, Loewen G. HER-2/neu protein expression and gene alteration in stage I-IIIA non-small-cell lung cancer: a study of 140 cases using a combination of high throughput tissue microarray, immunohistochemistry, and fluorescent in situ hybridization. Diagn Mol Pathol. 2003 Dec;12(4):201-11

Zhou H, Randall RL, Brothman AR, Maxwell T, Coffin CM, Goldsby RE. Her-2/neu expression in osteosarcoma increases risk of lung metastasis and can be associated with gene amplification. J Pediatr Hematol Oncol. 2003 Jan;25(1):27-32

Al Moustafa AE, Foulkes WD, Benlimame N, Wong A, Yen L, Bergeron J, Batist G, Alpert L, Alaoui-Jamali MA. E6/E7 proteins of HPV type 16 and ErbB-2 cooperate to induce neoplastic transformation of primary normal oral epithelial cells. Oncogene. 2004 Jan 15;23(2):350-8

Bernard C, Corzo G, Adachi-Akahane S, Foures G, Kanemaru K, Furukawa Y, Nakajima T, Darbon H. Solution structure of ADO1, a toxin extracted from the saliva of the assassin bug, Agriosphodrus dohrni. Proteins. 2004 Feb 1;54(2):195-205

Camilleri-Broët S, Hardy-Bessard AC, Le Tourneau A, Paraiso D, Levrel O, Leduc B, Bain S, Orfeuvre H, Audouin J, Pujade-Lauraine E. HER-2 overexpression is an independent marker of poor prognosis of advanced primary ovarian carcinoma: a multicenter study of the GINECO group. Ann Oncol. 2004 Jan;15(1):104-12

Casalini P, Iorio MV, Galmozzi E, Ménard S. Role of HER receptors family in development and differentiation. J Cell Physiol. 2004 Sep;200(3):343-50

Chung GG, Zerkowski MP, Ocal IT, Dolled-Filhart M, Kang JY, Psyrri A, Camp RL, Rimm DL. beta-Catenin and p53 analyses of a breast carcinoma tissue microarray. Cancer. 2004 May 15;100(10):2084-92

Cianciulli A, Cosimelli M, Marzano R, Merola R, Piperno G, Sperduti I, de la Iglesia F, Leonardo G, Graziano F, Mancini R, Guadagni F. Genetic and pathologic significance of 1p, 17p, and 18q aneusomy and the ERBB2 gene in colorectal cancer and related normal colonic mucosa. Cancer Genet Cytogenet. 2004 May;151(1):52-9

Essapen S, Thomas H, Green M, De Vries C, Cook MG, Marks C, Topham C, Modjtahedi H. The expression and prognostic significance of HER-2 in colorectal cancer and its relationship with clinicopathological parameters. Int J Oncol. 2004 Feb;24(2):241-8

Hermanová M, Lukás Z, Nenutil R, Brázdil J, Kroupová I, Kren L, Pazourková M, Růzicka M, Díte P. Amplification and overexpression of HER-2/neu in invasive ductal carcinomas of the pancreas and pancreatic intraepithelial neoplasms and the relationship to the expression of p21(WAF1/CIP1). Neoplasma. 2004;51(2):77-83

Hirsch FR, Langer CJ. The role of HER2/neu expression and trastuzumab in non-small cell lung cancer. Semin Oncol. 2004 Feb;31(1 Suppl 1):75-82

Hughes DP, Thomas DG, Giordano TJ, Baker LH, McDonagh KT. Cell surface expression of epidermal growth factor receptor and Her-2 with nuclear expression of Her-4 in primary osteosarcoma. Cancer Res. 2004 Mar 15;64(6):2047-53

Konecny GE, Thomssen C, Lück HJ, Untch M, Wang HJ, Kuhn W, Eidtmann H, du Bois A, Olbricht S, Steinfeld D, Möbus V, von Minckwitz G, Dandekar S, Ramos L, Pauletti G, Pegram MD, Jänicke F, Slamon DJ. Her-2/neu gene amplification and response to paclitaxel in patients with metastatic breast cancer. J Natl Cancer Inst. 2004 Aug 4;96(15):1141-51

Lassus H, Leminen A, Vayrynen A, Cheng G, Gustafsson JA, Isola J, Butzow R. ERBB2 amplification is superior to protein expression status in predicting patient outcome in serous ovarian carcinoma. Gynecol Oncol. 2004 Jan;92(1):31-9

Mándoky L, Géczi L, Bodrogi I, Tóth J, Csuka O, Kásler M, Bak M. Clinical relevance of HER-2/neu expression in germ-cell testicular tumors. Anticancer Res. 2004 Jul-Aug;24(4):2219-24

Onn A, Correa AM, Gilcrease M, Isobe T, Massarelli E, Bucana CD, O'Reilly MS, Hong WK, Fidler IJ, Putnam JB, Herbst RS. Synchronous overexpression of epidermal growth factor receptor and HER2-neu protein is a predictor of poor outcome in patients with stage I non-small cell lung cancer. Clin Cancer Res. 2004 Jan 1;10(1 Pt 1):136-43

Riener EK, Arnold N, Kommoss F, Lauinger S, Pfisterer J. The prognostic and predictive value of immunohistochemically detected HER-2/neu overexpression in 361 patients with ovarian cancer: a multicenter study. Gynecol Oncol. 2004 Oct;95(1):89-94

Stephens P, Hunter C, Bignell G, Edkins S, Davies H, Teague J, Stevens C, O'Meara S, Smith R, Parker A, Barthorpe A, Blow M, Brackenbury L, Butler A, Clarke O, Cole J, Dicks E, Dike A, Drozd A, Edwards K, Forbes S, Foster R, Gray K, Greenman C, Halliday K, Hills K, Kosmidou V, Lugg R, Menzies A, Perry J, Petty R, Raine K, Ratford L, Shepherd R, Small A, Stephens Y, Tofts C, Varian J, West S, Widaa S, Yates A, Brasseur F, Cooper CS, Flanagan AM, Knowles M, Leung SY, Louis DN, Looijenga LH, Malkowicz B, Pierotti MA, Teh B, Chenevix-Trench G, Weber BL, Yuen ST, Harris G, Goldstraw P, Nicholson AG, Futreal PA, Wooster R, Stratton MR. Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature. 2004 Sep 30;431(7008):525-6

Castiglioni F, Tagliabue E, Campiglio M, Pupa SM, Balsari A, Ménard S. Role of exon-16-deleted HER2 in breast carcinomas. Endocr Relat Cancer. 2006 Mar;13(1):221-32

Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008 Sep;19(9):1523-9

Hansel DE, Swain E, Dreicer R, Tubbs RR. HER2 overexpression and amplification in urothelial carcinoma of the bladder is associated with MYC coamplification in a subset of cases. Am J Clin Pathol. 2008 Aug;130(2):274-81

Jo UH, Han SG, Seo JH, Park KH, Lee JW, Lee HJ, Ryu JS, Kim YH. The genetic polymorphisms of HER-2 and the risk of lung cancer in a Korean population. BMC Cancer. 2008 Dec 4;8:359

Yoshikawa D, Ojima H, Iwasaki M, Hiraoka N, Kosuge T, Kasai S, Hirohashi S, Shibata T. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. Br J Cancer. 2008 Jan 29;98(2):418-25

Hirsch FR, Varella-Garcia M, Cappuzzo F. Predictive value of EGFR and HER2 overexpression in advanced non-small-cell lung cancer. Oncogene. 2009 Aug;28 Suppl 1:S32-7

Mitra D, Brumlik MJ, Okamgba SU, Zhu Y, Duplessis TT, Parvani JG, Lesko SM, Brogi E, Jones FE. An oncogenic

isoform of HER2 associated with locally disseminated breast cancer and trastuzumab resistance. Mol Cancer Ther. 2009 Aug;8(8):2152-62

Higa GM, Singh V, Abraham J. Biological considerations and clinical applications of new HER2-targeted agents. Expert Rev Anticancer Ther. 2010 Sep;10(9):1497-509

Kimple RJ, Vaseva AV, Cox AD, Baerman KM, Calvo BF, Tepper JE, Shields JM, Sartor CI. Radiosensitization of epidermal growth factor receptor/HER2-positive pancreatic cancer is mediated by inhibition of Akt independent of ras mutational status. Clin Cancer Res. 2010 Feb 1;16(3):912-23

Tai W, Mahato R, Cheng K. The role of HER2 in cancer therapy and targeted drug delivery. J Control Release. 2010 Sep 15;146(3):264-75

Williams MD, Roberts DB, Kies MS, Mao L, Weber RS, El-Naggar AK. Genetic and expression analysis of HER-2 and EGFR genes in salivary duct carcinoma: empirical and therapeutic significance. Clin Cancer Res. 2010 Apr 15;16(8):2266-74

Arribas J, Baselga J, Pedersen K, Parra-Palau JL. p95HER2 and breast cancer. Cancer Res. 2011 Mar 1;71(5):1515-9

Gutierrez C, Schiff R. HER2: biology, detection, and clinical implications. Arch Pathol Lab Med. 2011 Jan;135(1):55-62

Shan LQ, Ma S, Qiu XC, Wang T, Yu SB, Ma BA, Zhou Y, Fan QY, Yang AG. A novel recombinant immuno-tBid with a furin site effectively suppresses the growth of HER2-positive osteosarcoma cells in vitro. Oncol Rep. 2011 Feb;25(2):325-31

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