Gene Focus

Concise expert focus on a gene at the heart of pharmacogenomic research

Focus on *ERBB2*

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Highlights

- *ERBB2* is commonly amplified in breast tumors.
- The overexpressed ERBB2 protein is the target of trastuzumab and lapatinib, two drugs currently used in clinical practice.
- *ERBB2* is unlikely to be a breast cancer predisposition gene.
- There are, at present, no known genetic polymorphisms in *ERBB2* that affect the binding, efficacy or tolerability of trastuzumab or lapatinib.
- Lapatinib pharmacokinetics could be altered in individuals carrying polymorphisms in the genes coding for the hepatic cytochrome 2C19 or for the transporter P-glycoprotein.

The *ERBB2* (HER2) gene codes for a tyrosine kinase receptor that activates pathways involved in cell division, differentiation and apoptosis. Gene amplification, and as a result protein overexpression, are commonly seen in breast tumors and correlate with poor prognosis. The overexpressed protein is the target of trastuzumab, a monoclonal antibody routinely used in clinical practice. A new tyrosine kinase inhibitor, lapatinib, is already an alternative in women progressing despite treatment with trastuzumab. Using comprehensive tagging approaches, highly-powered association studies concluded that *ERBB2* was unlikely to be a breast cancer predisposition gene. *ERBB2* pharmacogenomics are of little relevance at present, since we have no knowledge of polymorphisms in the gene that could affect the binding, efficacy or tolerability of trastuzumab or lapatinib. There is minor contribution from hepatic cytochrome CYP2C19 to the metabolism of lapatinib, whereas *in vitro* studies have shown the drug to be a substrate for the transporter P-glycoprotein. If, and how, the pharmacokinetics of lapatinib would be altered in individuals carrying polymorphisms in *CYP2C19* or *ABCB1* – the gene that codes for the P-glycoprotein – is yet to be determined.

The *ERBB2* (HER2) gene is located on chromosome 17q12-q21, spans 38 kb, and comprises 27 coding exons, which code for a 185-kilodalton protein. *ERBB2* amplification is seen in 14–34% of breast tumors and correlates with protein overexpression [1–6]. Amplification of *ERBB2* in breast tumors is of particular relevance in the clinical setting, as it has prognostic implications; it correlates with higher tumor grade [1,4–6], positive nodal status [3], metastatic disease [6], hormone receptor negativity [1,3,5], low receptor levels and resistance to hormone therapy in hormone-receptor-positive tumors [2,7,8], disease relapse [4,9] and disease-related death [1,4,9]. Clinical data have led to the development of a monoclonal antibody binding to the extracellular domain of the ERBB2 protein, trastuzumab (Herceptin®) [10], which is now routinely used in combination with chemotherapy in patients with

ERBB2-amplified breast cancer [11]. Lapatinib, a new molecule that inhibits the tyrosine kinases of EGFR and ERBB2, is already an alternative in women who are progressing after treatment with trastuzumab [12].

ERBB2 is one of four members of the ERBB tyrosine kinase receptor family, the other members being EGFR (ERBB1), ERBB3 and ERBB4 [13]. The four ERBBs share an overall structure of an extracellular region involved in receptor dimerization and ligand binding, a transmembrane region anchoring the receptor at the membrane and an intracellular carboxy-terminal tail with tyrosine autophosphorylation sites [14]. ERBB receptors form homo- and hetero-dimers. Dimerization is induced by ligands such as neuregulins and epidermal growth factor, and leads to transactivation and tyrosine phosphorylation at sites in the cytoplasmic domain [13,14].

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When phosphorylated, these sites activate signaling pathways that contribute to cell division, migration, adhesion, differentiation and apoptosis.

ERBB2 plays a key role in the ERBB pathway. It is a more potent oncoprotein than the other ERBBs and has been shown to be the preferred dimerization partner of the other three other members [15]. Amplification of the *ERBB2* gene and overexpression of the protein are important mechanisms of oncogene activation in breast cancer. As the number of ERBB2 receptors increases in cancer cells, the equilibrium between ERBB homo- and hetero-dimers is shifted even more towards potent ERBB2-containing hetero-dimers [13]. Downstream signaling is thus enhanced, and tumor cells gain a strong proliferative advantage, as illustrated by the poor prognosis associated with breast tumors with *ERBB2* amplification. Like overexpression of the normal gene, genetic variation in the sequence coding for the transmembrane region can activate ERBB2 transforming properties; a mutation resulting in a valine to glutamic acid substitution at position 659 increases transforming activity *in vitro* [16], while a single point mutation at residue 664 has been shown to activate neu, the rat homolog of ERBB2 [17].

A potentially functional common SNP that is predicted *in silico* to increase protein kinase activity has been identified in the transmembrane region of the ERBB2 protein at codon 655 (rs1801200, ATC/Isoleucine to GTC/Valine [I655V]) [18,19]. An early report of a borderline association between the rare allele and breast cancer susceptibility generated much interest [20]. However, all but one subsequent study failed to replicate this association [21–36]. This suggests that initial positive findings were due to type I statistical errors. More recently, two publications used a comprehensive tagging approach to study common genetic variation across the whole gene, and concluded that *ERBB2* was not associated with breast cancer susceptibility [34,35].

Very little is known about ERBB2 pharmacogenomics. In April 2007, a PubMed search using the MeSH terms ‘ERBB2’ and ‘pharmacogenomics’ only yielded three hits, none of them actually addressing the issue (the potential impact of variation across the gene on response to drugs targeting the protein). The first article discusses the potential implications of somatic – not germline – mutations on the development of new drugs [37], while the others are reviews of pharmacogenomics in general [38], and of genetic amplification as a tool for selecting therapeutic strategies [39]. An updated search carried out weeks before the publication of this review failed to produce more relevant results. Han *et al.* recently found an association between the haplotype tagged by the common alleles of coding SNPs I655V and A1170P (rs1058808) and ERBB2 protein expression [40]. This association, if it were to be replicated, could mean that women carrying this haplotype would be more likely to respond to trastuzumab. Unfortunately, such findings are unlikely to be relevant, as gene amplification or protein expression, and not haplotype status, will remain the factors that determine who may, or may not, benefit from trastuzumab therapy.

What do the respective mechanisms of action of trastuzumab and lapatinib tell us about the relevance of pharmacogenomics for patients treated with these drugs? The segment of *ERBB2* coding for the extracellular domain targeted by trastuzumab contains rs4252633, a rare, nonsynonymous coding SNP whose functional consequences are unknown [101,102]. It is theoretically possible that, if this SNP was found to be functional, the different amino acid coded by the rare allele could affect the binding of trastuzumab, or any other future drug targeting the ERBB2 extracellular domain. Lapatinib down-regulates tyrosine phosphorylation by binding to the ATP-binding cleft [41]. No coding SNPs have been identified in this region as yet, and it is therefore unlikely that genetic variation in *ERBB2* will affect the efficacy or safety profile of

lapatinib, or any other tyrosine kinase inhibitors [42,101,102].

Finally, SNPs coding for hepatic cytochromes (CYP) or cell surface transporters should not affect trastuzumab pharmacokinetics as it does not appear to be metabolized by CYP 2C9, 2C19 or 2D6, or to be substrate for the P-glycoprotein. However, there seems to be minor contribution from CYP2C19 to the metabolism of lapatinib, whereas *in vitro* studies have shown that the drug was a substrate for the P-glycoprotein [43,103]. If, and how, the pharmacokinetics of lapatinib would be altered in individuals carrying polymorphisms in *CYP2C19* or *ABCB1* – the gene that codes for P-glycoprotein – is yet to be determined.

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