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Journals Club

Review of: The rare ERBB2 variant Ile654Val is associated with an increased familial breast cancer risk

I. G. Campbell

Peter MacCallum Cancer Centre, East Melbourne, Vic., Australia.

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B. Frank, K. Hemminki, M. Wirtenberger, J. L. Bermejo, P. Bugert, R. Klaes, R. K. Schmutzler, B. Wappenschmidt, C. R. Bartram, B. Burwinkel. The rare ERBB2 variant Ile654Val is associated with an increased familial breast cancer risk. ***Carcinogenesis*** 2005; **26**: 643–7.

Abstract of the original article
Overexpression of the proto-oncogene *ERBB2* (HER2/NEU) has been observed in 20–30% of breast cancers involving poor prognosis. Genetic alterations within *ERBB2* have been shown to induce carcinogenesis and metastasis. We investigated eight annotated single nucleotide polymorphisms for occurrence in familial breast cancer samples. The confirmed variants Ile654Val, Ile655Val and Ala1170Pro were analysed in subsequent epidemiological studies on familial breast cancer risk. While Ala1170Pro resides within a C-terminally located regulatory domain, the two adjacent polymorphisms Ile654Val and Ile655Val are part of the transmembrane domain. A case–control study analysing a cohort of 348 German familial breast cancer cases and 960 corresponding controls showed no significant association of either Ile655Val (OR = 1.05, 95% CI = 0.82–1.34, $P = 0.728$) or Ala1170Pro (OR = 0.94, 95% CI = 0.74–1.20, $P = 0.632$) with familial breast cancer risk. Differences in haplotype frequencies between cases and controls could also not be detected. The ERBB2 variant Ile654Val, however, revealed an increased risk for carriers of the heterozygous Val654 allele (OR = 2.56, 95% CI = 1.08–6.08, $P = 0.028$). The rare Val654 variant is linked with the more frequent Val655, resulting in two consecutive valine instead of two isoleucine residues within the transmembrane domain. Computational analyses suggest that the Val654–Val655 allele provokes receptor dimerisation and activation, thus stimulating kinase activity and cell transformation. We hypothesise that ERBB2 Val654 represents an oncogenic variant which might, in addition, influence clinical outcome and predict a worse prognosis.

Review

Human epidermal growth factor receptor 2 (*HER2*) is a transmembrane glycoprotein with tyrosine kinase activity that has several functions, including the control of cellular proliferation. Overexpression of *HER2* is detected in a large proportion of breast cancers [1,2] indicating that activation of this gene is an important step in breast carcinogenesis. The use of a recombinant humanised monoclonal antibody that specifically targets HER2 may increase the clinical benefit of first-line chemotherapy in women with breast cancers that overexpress *HER2* [3]. Consequently, it is plausible that functional polymorphisms in this gene that enhance HER2 activity may represent breast cancer predisposing alleles.

Correspondence to: A/Prof. Ian Campbell, VBCRC Cancer Genetics Laboratory, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Melbourne, Victoria 8006, Australia. E-mail: ian.campbell@petermac.org; Tel: +61 3 96561803; Fax: +61 3 96561411

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The first indication that breast cancer predisposing HER2 alleles may indeed exist stemmed from a report that an isoleucine to valine polymorphism at codon 655 (Ile655Val) was associated with an increased risk of breast cancer in a Chinese population [4]. The flurry of studies that followed yielded conflicting conclusions regarding the Ile655Val polymorphism [5–10] but a few yielded positive associations with the Val655 allele. Interestingly, in the two that reported a positive association, the only effect evident was in women diagnosed before age 45 years [4] or in women with a first degree family history of breast cancer [6], groups in which inherited genetic effects on susceptibility are expected to be more pronounced. However, none of the recent studies, which have used much larger cohorts, have reported a positive association of the Val655 allele with breast cancer [11–13], and indeed two studies reported an inverse association with risk [12,13]. The conclusion from these studies is that the Ile655Val polymorphism is unlikely to be involved in breast cancer predisposition and by implication the *HER2* gene itself. However, this article suggests that the previously ignored Ile654Val polymorphism, which is adjacent to Ile655Val, may represent an oncogenic variant and might also explain the contradictory findings of previous cancer association studies.

The Ile654Val variant was found to be associated with an increased risk of breast cancer with an odds ratio of 2.56. However, the 95% confidence interval is wide (1.08–6.08) due to the fact that the number of cases are relatively modest ($n = 347$) and the valine allele is very rare (just 0.006 in the German control population). Consequently, the study is highly prone to type I statistical error. Indeed, applying the arguably more appropriate Fishers exact test (rather than the χ^2 test used) the *P*-value is of marginal significant at 0.042. Clearly further studies will be required in independent and larger populations to have confidence that the association is *bona fide*.

However, an important discovery of the study that lends credence to the positive association, is the fact that the Val654 is linked to Val655, which results in two consecutive valines instead of two isoleucines. Both isoleucine residues are highly conserved across species and computational analysis suggested that the combined substitution of both Ile654 and Ile655 residues with valine would stabilise the formation of activated HER2 homodimers. This has important implications with regard to previous Ile655Val polymorphism studies. The suggestion is that while the more common Val655 allele might also be expected to stabilise dimerisation, the effect would only be sufficiently powerful to influence breast cancer risk when in combination with the Val654 allele. Therefore, the extent to which any study would identify a cancer association would be dependent on the frequency of the Val654 polymorphism in different ethnic populations. A further implication is that many studies of the Ile655Val polymorphism have used single nucleotide polymorphism (SNP) typing methodologies that would be compromised by the existence of the Ile654Val allele, although given its rarity, it seems unlikely that this would have a major impact on the overall genotype frequencies.

In conclusion, this article has identified a potentially important new association and offers a plausible explanation for previous failures to substantiate a cancer predisposing role for *HER2*. The hypothesised functional consequences of the combined Val654–Val655 haplotype should be easily verifiable *in vitro* and no doubt investigators will now be tooling up to re-analyse their data-sets in light of this new information.

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