Letter

Co-incidental increase in gene copy number of *ERBB2* and *LRIG1* in breast cancer

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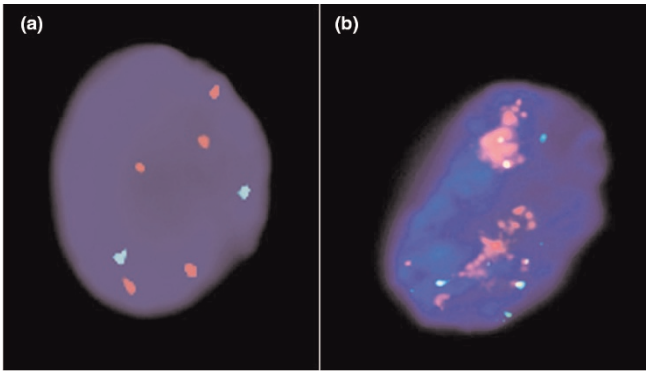
Using fluorescence *in situ* hybridization (FISH), we previously showed that the *LRIG1* gene had an increased copy number in 11 of 28 (39%) breast cancer tumours [1]. The *LRIG1* gene (leucine-rich repeats and immunoglobulin-like domains 1) at chromosome 3p14 is a proposed tumour suppressor gene that negatively regulates various receptor tyrosine kinases, including the breast cancer proto-oncogene product ERBB2 [2,3].

Recently, however, Miller and colleagues [4] showed that 10 of 13 (76%) ERBB2$^+$ tumours had decreased LRIG1 protein levels compared to normal breast tissue. As their data showed down-regulation at the protein level whereas our data showed an increased copy number at the genomic level, we analysed 45 additional breast tumours by FISH as previously described [1]. Thus, out of 73 tumours analysed to date, 25 (34%) did indeed have increased *LRIG1* copy number. To further analyse the relationship between *LRIG1* and *ERBB2* at the genomic level, we evaluated the *ERBB2* gene copy numbers in 18 tumours with increased *LRIG1* copy number using FISH analysis according to standard procedures. Interestingly, 16 (89%) out of the 18 tumours displayed increased copy number of *ERBB2* (Figure 1). This suggests that the majority of breast cancer tumours with increased copy number of *ERBB2* simultaneously had increased *LRIG1* copy number (our data) and decreased LRIG1 protein levels [4].

We draw the following major conclusions from these results. First, as previously shown, a significant proportion of breast tumours have an increased *LRIG1* gene dosage. Second, there is a correlation between increased gene copy numbers of *ERBB2* and *LRIG1*. Third, based on the Miller protein data, most of the tumours with increased *LRIG1* gene dosage express reduced levels of the LRIG1 protein. This indicates a negative selection against LRIG1 protein expression, supporting the notion that *LRIG1* is a tumour suppressor in breast cancer. Although the mechanism behind the down-regulation of LRIG1 protein in breast cancer is not known, it has been reported that increased gene copy

Figure 1



Increased copy number of *LRIG1* and *ERBB2* in human breast cancer in the same patient. Interphase nuclei from a breast cancer tumour were analysed by FISH. **(a)** A specific *LRIG1* probe (red) showed increased *LRIG1* copy number (five copies) whereas a specific centromere probe (CEP3) (green) showed normal chromosome 3 copy number (two copies). **(b)** A specific *ERBB2* probe (red) showed amplification of the *ERBB2* gene whereas a specific centromere probe (CEP17; green) showed three copies of chromosomes 17.

FISH = fluorescence *in situ* hybridization.

numbers in some cases are associated with decreased mRNA expression [5]. In any case, the high frequency (34%) of tumours with increased *LRIG1* gene copy number implies a positive selection for tumour cells with this genomic alteration. It remains, however, to be elucidated whether the molecular driver behind the selective advantage associated with this alteration is LRIG1 down-regulation *per se*. Other possibilities include activation of nearby proto-oncogenes or the generation of novel oncogenic fusion genes.

In summary, the co-incidental increase in copy number of *ERBB2* and *LRIG1* in breast cancer is a novel finding, pointing at a functional co-operation between these genetic events, where the biological and clinical importance need to be clarified further.

Competing interests

The authors declare that they have no competing interests.

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