Commentary

Genes harbouring susceptibility SNPs are differentially expressed in the breast cancer subtypes

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Abstract

Recently, genome-wide association studies of breast cancer revealed single nucleotide polymorphisms (SNPs) in five genes with novel association to susceptibility. While there is little doubt that the novel susceptibility markers produced from such highly powered studies are true, the mechanisms by which they cause the susceptibility remain undetermined. We have looked at the expression levels of the identified genes in tumours and found that they are highly significantly differentially expressed between the five established breast cancer subtypes. Also, a significant association between SNPs in these genes and their expression in tumours was seen as well as a significantly different frequency of the SNPs between the subtypes. This suggests that the observed genes are associated with different breast cancer subtypes, and may exert their effect through their expression in the tumours. Thus, future studies stratifying patients by their molecular subtypes may give much more power to classic case control studies, and genes of no or borderline significance may appear to be high-penetrant for certain subtypes and, therefore, be identifiable.

A genome-wide association study of breast cancer has revealed single nucleotide polymorphisms (SNPs) in five genes with novel association to susceptibility: *TNRC9*, *FGFR2*, *MAP3K1*, *H19* and *LSP1* [1]. The results were confirmed for *FGFR2* and *TNRC9* in two independent studies [2,3]. However, these studies revealed little of the mechanisms underlying these associations. Pooling of such a large amount of cases, as performed in these studies, inevitably leads to concealment of the various histological and clinico-pathological subtypes. This suggests that the observed genes are either of universal importance for breast cancer development, are associated with a subgroup that dominates the overall pool or are associated with any subgroup but with an association sufficiently strong to dominate the overall result. Breast cancer patients can be divided into five distinct molecular subtypes based on their expression profiles [4]. The existence of these five subtypes, luminal A, luminal B, basal-like, ErbB2$^+$, and normal-like, have been confirmed in independent datasets [5] and they are associated with different clinical outcomes [6]. If the probability to develop a given subtype of breast cancer is genetically determined, we might expect to find that the newly discovered susceptibility genes [1] are differentially expressed in the various tumour subtypes, and that their transcription is regulated *in cis* by SNPs within them. With this in mind, we retrieved the mRNA expression data of *TNRC9*, *FGFR2*, *MAP3K1*, *H19* and *LSP1* from 112 breast tumours representing all five subtypes [7]. Significantly different mRNA levels between the subtypes were found for all the five genes by ANOVA analysis (Table 1). For instance, *TNRC9* was up-regulated in luminal A, luminal B and ErbB2$^+$ subtypes and down-regulated in the basal-like subtype ($p = 4.5 \times 10^{-7}$). *FGFR2* was up-regulated in luminal A and basal-like subtypes and down-regulated in luminal B and ErbB2$^+$ subtypes ($p = 3.1 \times 10^{-5}$), while *MAP3K1* was up-regulated in luminal A and the normal-like subtypes and down-regulated in luminal B, ErbB2$^+$ and basal-like subtypes ($p = 5.2 \times 10^{-5}$). Furthermore, we could calculate the association between SNPs residing within these genes and their tumour expression levels since genotype data on these patients have been generated using an Illumina 109K SNP array. The three genes whose expression levels were most significantly associated with tumour subtype (*TNRC9*, *FGFR2* and *MAP3K1*) all harboured SNPs within them displaying a significant association with gene expression level (Table 1). One of these SNPs, rs9940048 in *TNRC9*, displayed a significantly different genotype distribution between the subtypes, with breast cancer patients homozygous for the low frequency allele over-represented in the basal-like subtype ($p = 0.003$), in concordance with the

SNP = single nucleotide polymorphism.

Table 1

***P*-values after ANOVA analyses**

Gene	Clone ID	SNP ID	Exp vs subtype[a]	SNP vs Exp[b]	SNP vs subtype[c]
TNRC9	IMAGE:2139448	rs9940048	4.5×10^{-7}	0.043	0.003
FGFR2	IMAGE:809464	rs2981451	3.1×10^{-5}	0.035	0.875
MAP3K1	IMAGE:810230	rs831818	5.2×10^{-5}	0.0045	0.779
H19	IMAGE:428721	rs2839701	0.001	0.268	0.082
LSP1	IMAGE:110788	rs661348	0.005	0.840	0.56

[a]Expression levels of the five genes (clone ID) between the various subgroups. [b]Single nucleotide polymorphisms (SNP ID) versus expression of the five genes. [c]Genotype distribution of SNPs (SNP ID) between the various subgroups.

observation that the basal-like tumours had the lowest levels of *TNRC9* mRNA.

Conclusions

Our results suggest that SNPs in the recently discovered susceptibility genes may exert their effect through the expression of their genes in tumours, giving rise to the various breast cancer subtypes. Thus, stratification of patients by their molecular subtypes may give much more power to classic case control studies, and genes of no or borderline significance may appear to be high-penetrant for certain subtypes and, therefore, be identifiable.

Competing interests

The authors declare that they have no competing interests.

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