Low Frequency of Somatic Mutations in the LKBI/Peutz-Jeghers Syndrome Gene in Sporadic Breast Cancer

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Abstract

Germ-line mutations in the LKBI gene on chromosome 19p are responsible for most cases of the Peutz-Jeghers syndrome, in which intestinal hamartomas are associated with elevated risks of several cancer types, including breast cancer. We have evaluated the role of somatic mutations in LKBI in breast cancer. Of 40 informative primary breast cancers, 3 showed loss of heterozygosity on chromosome 19p in the vicinity of LKBI, and no somatic mutations of LKBI were observed in 62 primary breast cancers and 17 established breast cancer cell lines. The results indicate that mutations in LKBI do not play an important role in the development of sporadic breast cancer.

Introduction

PJS2 is a rare, autosomal dominantly inherited condition characterized by benign intestinal hamartomas and melanin spots of the lips, buccal mucosa, and digits (1). Following the demonstration of chromosome 19p allele loss in intestinal hamartomas from PJS patients, the PJS gene was formally mapped by genetic linkage analysis to chromosome 19p (2). The gene was recently identified as LKBI, which encodes a widely expressed, serine/threonine kinase of 433 amino acids that is highly conserved in mouse and Xenopus (3). The large majority of mutations in LKBI detected in PJS families are predicted to truncate the protein and hence inactivate it. Although germ-line mutations in genes encoding other protein kinases such as ret (4), met (5), and cdk4 (6) are associated with predisposition to neoplasia, in these cases the mutations result in activation of kinase activity. LKBI is therefore the first known protein kinase that predisposes to cancer when it is inactivated.

In addition to intestinal hamartomas, PJS is also associated with an increased risk of several different types of neoplasms, including gastrointestinal, ovarian, pancreatic, and breast cancers (1, 7, 8). None of these risks, including that of breast cancer, have been precisely estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated. However, in a recent review of published series, five breast cancers diagnosed by age 41 were observed in PJS patients, with estimated.
results suggest that mutations in this gene do not play a substantial role in the genesis of sporadic breast cancer.

The tumor suppressor gene/recessive oncogene hypothesis articulated and elaborated by Knudson predicts that genes that confer a risk of cancer as a result of germ-line mutations are likely to be somatically mutated in sporadic cancers of the same type (15). This has proved to be the case for the paradigm of the RBL gene and for several other genes, such as VHL and NF2. LKB1 does not appear to conform to this model. Although it can be argued that the risk of breast cancer conferred by LKB1 mutations is relatively small, it is interesting that the model does not apply to a number of other breast cancer susceptibility genes that confer greater risks. For example, truncating mutations in BRCA1 and BRCA2 confer a high risk of breast cancer, but hardly any somatic mutations in sporadic breast cancers have been reported in either gene (16, 17). Similarly, germ-line mutations in the PTEN/MMAC1 gene confer an elevated risk of breast cancer in individuals with Cowden’s disease, but some mutations of PTEN have been identified in only 6% (4 of 65) of breast cancer cell lines and xenografts and 2% (1 of 50) of primary breast cancers (18, 19). The notable exception to this pattern is the p53 gene, in which germ-line mutations predispose to early-onset breast cancer in the Li-Fraumeni syndrome, and somatic mutations are observed in 20–50% of sporadic breast cancers (20).

The reasons for the low frequency in sporadic breast cancer of somatic mutations in BRCA1, BRCA2, PTEN/MMAC, and LKB1 compared to the high frequency of mutations in p53 are unclear: (a) it is possible (although in our view implausible) that these genes are more resistant to somatic mutation than p53; (b) the growth advantage conferred by inactivating mutations in BRCA1, BRCA2, PTEN/MMAC, and LKB1 (either directly by interference with control of cell proliferation and cell death or indirectly by inactivation of DNA repair processes) is relatively small. Indeed, carriers of BRCA1, BRCA2, PTEN/MMAC, or LKB1 germ-line mutations tend to develop none, or a small number of breast cancers despite the presence of the mutation in the whole breast epithelium. However, carriers of germ-line mutations in p53 also tend to develop only a small number of breast cancers, and somatic mutations in sporadic breast cancers are common; and (c) it is plausible that mutations in any cancer gene only contribute to oncogenesis in the correct cellular context and that the factors that define this context are more restricted for BRCA1, BRCA2, LKB1, and PTEN/MMAC than for p53. Such factors could be biological, e.g., a short period during development such as puberty when relatively few somatic mutations in these genes have occurred.

Either way, it appears that breast cancers arising in most known predisposition syndromes take a route to oncogenesis that is distinct from most sporadic cancers. It remains possible, of course, that BRCA1, BRCA2, LKB1, and PTEN/MMAC are altered in ways other than somatic mutation in sporadic cancers, such as regulation of mRNA levels. Alternatively, genes that encode other components of biological pathways which include BRCA1, BRCA2, LKB1, and PTEN/MMAC, may commonly be somatically mutated in sporadic breast cancers.

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References


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