Genotype-Phenotype Correlations in Breast Cancer

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KEYWORDS

• Genotype-phenotype • Breast cancer • Molecular • IDH2

Key points

- Of the many breast cancer histologic subtypes recognized by WHO, only a few harbor known recurrent genetic alterations associated with a specific morphology.
- Secretory carcinoma, adenoid cystic carcinoma, invasive lobular carcinoma, and the recently defined solid papillary carcinoma with reverse polarity have unique morphologic features and exhibit characteristic recurrent genetic abnormalities.
- Identifying the genetic underpinnings of breast cancer subytpes permits more accurate diagnosis and may provide new therapeutic targets.

ABSTRACT

Only a few breast cancer histologic subtypes harbor distinct genetic alterations that are associated with a specific morphology (genotype-phenotype correlation). Secretory carcinomas and adenoid cystic carcinomas are each characterized by recurrent translocations, and invasive lobular carcinomas frequently have *CDH1* mutations. Solid papillary carcinoma with reverse polarity is a rare breast cancer subtype with a distinctive morphology and recently identified *IDH2* mutations. We review the clinical and pathologic features and underlying genetic alterations of those breast cancer subtypes with established genotype-phenotype correlations and discuss the phenotypes associated with germline mutations in genes associated with hereditary breast cancer.

OVERVIEW

Genotype-phenotype correlation (ie, a recurrent genetic abnormality associated with a specific morphology) is relatively common in some tumor types. For example, nearly half of the diagnostic entities described in the most recent edition of the *WHO Classification of Tumors of Soft Tissue and Bone* are associated with recurrent cytogenetic and/or molecular alterations.[1,2] Many hematopoietic and lymphoid neoplasms also have genetic abnormalities associated with a specific morphology, such as the *PML-RARA* fusion gene defining acute promyelocytic leukemia.[3]

In contrast, of the 21 breast cancer histologic subtypes defined by the World Health Organization (WHO),[4] few are known to harbor distinct recurrent genetic alterations. Secretory carcinomas and adenoid cystic carcinomas (ACCs) are characterized by recurrent *ETV6-NTRK3* and

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MYB-NFIB fusion genes, respectively,[5,6] and invasive lobular carcinomas commonly have somatic *CDH1* mutations.[7] Recently, a rare breast cancer subtype, solid papillary carcinoma with reverse polarity (SPCRP), was more fully defined.[8] These tumors display a unique morphology and are associated with a high frequency of *IDH2* R172 hotspot mutations.[8] Finally, breast cancers associated with germline mutations in some breast cancer susceptibility genes, particularly *BRCA1*, have a characteristic constellation of histologic findings in many cases.[9,10]

Here we provide an updated review of those breast cancer subtypes with established genotype-phenotype correlations. Special emphasis is placed on the newly described molecular features of SPCRP. We also discuss the phenotypes associated with germline mutations in genes associated with hereditary breast cancer.

SECRETORY CARCINOMA

Secretory carcinoma is an exceptionally rare special subtype that represents fewer than 0.02% of all breast cancers.[4] It was first described by McDivitt and Stewart[11] in 1966 as a distinct tumor occurring in children and, therefore, was originally named "juvenile carcinoma." After this initial case series, multiple reports of the tumor occurring in adults were described, prompting a change in terminology to secretory carcinoma.[12] Recent analyses from larger population-based databases including the National Cancer Data Base and the National Cancer Institute's Survival, Epidemiology, and End Results program have shown that secretory carcinoma largely affects older patients with a median age of approximately 53 to 54 years[13,14]; however, when compared with invasive ductal carcinoma of no special type (IDC), a greater proportion of younger women are diagnosed with secretory carcinoma.[14] Cases of secretory carcinoma arising in men also have been reported.[15,16]

The architecture of secretory carcinoma is typically microcystic (honeycomb), solid, or tubular, with many tumors containing a mixture of all 3 patterns. Some tumors display a peripheral papillary architecture, and central sclerosis is often observed. The edges of the cancer are often well-circumscribed with pushing borders, but more infiltrative areas may be seen. The tumor cells are polygonal with granular to foamy amphophilic cytoplasm, small bland nuclei, and few mitoses (**Fig. 1**). The histologic hallmark of secretory carcinoma is the presence of intracellular and extracellular eosinophilic secretions that are periodic acid-Schiff (PAS)-positive and diastase-resistant.

Secretory carcinoma typically lacks estrogen receptor (ER) and progesterone receptor (PR) expression, and is negative for human epidermal growth factor 2 (HER2) overexpression and amplification and is thus a "triple-negative" breast cancer. Jacob and colleagues[14] suggested that contrary to prior reports, up to 64% of secretory carcinomas may be positive for ER. However, major limitations of this study include the lack of both central histologic review and molecular status to confirm the diagnosis of secretory carcinoma. Furthermore, most ER-positive secretory carcinomas are reported to display only focal, weak ER immunoreactivity. Based on variable immunoreactivity with the basal cytokeratins (CK) 5/6 and/or CK14, as well as CD117 and epidermal growth factor receptor (EGFR), secretory carcinoma can be considered a basal-like carcinoma.[17] S100 protein and α-lactalbumin are consistently positive, although the latter stain is not used in current clinical practice. The tumor cells also show expression of mammaglobin, GATA3, and STAT5a, and are usually negative for

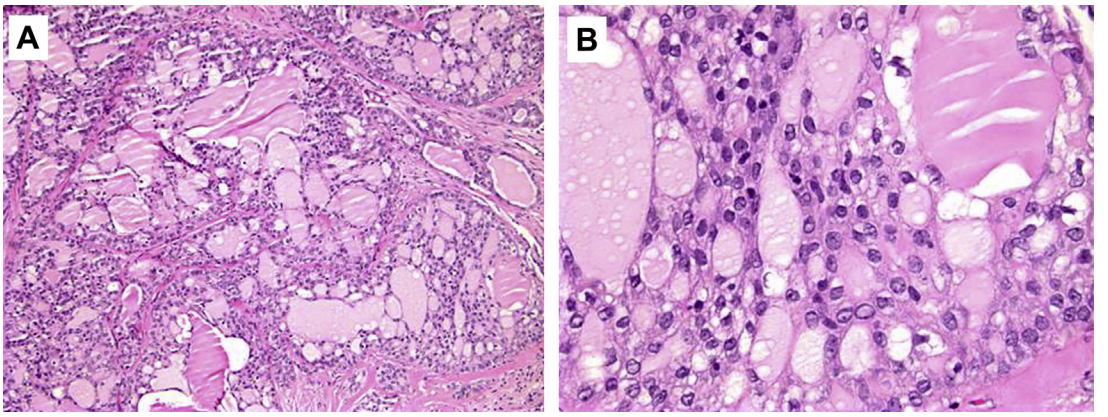

Fig. 1. Secretory carcinoma. (*A*) This tumor is composed of cribriform islands of cells with numerous glandular spaces containing eosinophilic secretions. (*B*) At higher power, the tumor cells have foamy cytoplasm and relatively uniform nuclei with variably prominent nucleoli.