Pathology and Somatic Alterations in Hereditary Lobular Breast Cancers

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Abstract

The most frequent special histological type of breast cancer is represented by invasive lobular carcinoma (ILC), which makes up about 15% of all invasive breast carcinomas. The molecular signature of ILC is the dysregulation of E-cadherin due to *CDH1* abnormalities. Although *CDH1* germline mutations are very uncommon in women with early-onset and/or familial ILC, they are the most common detrimental non-BRCA mutations and are thought to be the origin of a significant fraction of lobular breast cancer. Since the morphology and immunophenotype of hereditary and non-hereditary ILCs are nearly identical, no specific histopathological findings can be used to distinguish between the two. High-throughput sequencing studies revealed that ILCs represent a separate entity at the genomic level. This chapter addresses the very important topic of ILC morpho-molecular characteristics in the setting of germline and/or somatic *CDH1* abnormalities.

11.1 Introduction

Invasive lobular carcinoma (ILC) is the most common special type of breast cancer and accounts for ~15% of invasive breast carcinomas [1]. Dysregulation of E-cadherin due to *CDH1* aberrations is considered the molecular hallmark of ILC

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[2, 3]. Although the frequency of *CDH1* germline mutations is very low (~1%) in women with early-onset or familial ILC, these mutations represent the most frequent deleterious non-BRCA mutations, and they are considered founder genetic events in a substantial proportion of lobular breast cancer [4–6]. No specific histopathological features can help discriminate between hereditary and non-hereditary ILCs because their morphology and immunophenotype are substantially identical [7]. However, ILCs display peculiar clinic-pathologic characteristics as compared to other breast cancer histotypes [1]. Moreover, high-throughput sequencing analyses showed that ILCs also represent a distinct entity at the genomic level [2, 3, 8, 9]. This chapter provides a comprehensive overview of the morpho-molecular characteristics of ILC in the context of germline and/or somatic CDH1 aberrations.

11.2 Pathology of Lobular Breast Cancer

Individuals with ILC typically have a diagnosis at an older age and come to the physician's attention with larger tumors than patients with invasive breast cancer (IBC) of no special type [10]. Hereditary ILC is often bilateral and multicentric, appearing as ill-defined palpable mass(es) or widespread breast nodularities [11]. Classic ILC is composed of non-to-poorly cohesive small, roundish, monomorphic neoplastic elements, with uniform nuclei, inconspicuous nucleoli, and infrequent mitotic figures interspersed into a variably dense fibrous stroma arranged in loose or linear growth pattern. ILC exhibits a targetoid concentric distribution around ducts and lobules and is usually associated with little host reaction [1, 12–16].

It is possible to identify different ILC variants, including solid, alveolar, trabecular, tubule-lobular, signet ring cell, pleomorphic, and histiocytoid which differ from classical ILC in their morphologic characteristics and behavior (Fig. 11.1).

The traditional ILC and other ILC variants are occasionally mixed [13]. The discohesive tumor cells that make up the solid variant of ILC grow in solid nests and may exhibit pleomorphism or enhanced mitotic activity. The tumor cells of alveolar ILC are grouped in distinct clusters or aggregates of 20 cells or more, which are divided by thin fibrous septa. Tumor cells develop in bands thicker than two cells in the trabecular ILC. The tubule-lobular type of ILC has a hybrid tubular and lobular appearance. The growth pattern of pleomorphic ILC is identical to that of classic ILC, but the tumor cells exhibit increased cytological atypia and pleomorphism as well as a higher rate of mitosis [1, 12–16].

Classic ILC are of low or intermediate histological grade and the majority are characterized by the positivity of hormone receptors and lack of HER2 expression; however, HER2-positive and/or triple-negative (estrogen and progesterone receptor-negative and HER-2 negative) phenotypes have been reported, particularly in ILC variants [1, 12–18]. Consistently, more than 80% of ILCs fall into the category of luminal molecular subtypes according to gene expression profile studies [3, 19]. Her-2-enriched and basal-like lobular tumors are rare, usually of non-classic variant, and associated with a worse prognosis [20]. Similar to invasive ductal carcinoma (IDC),

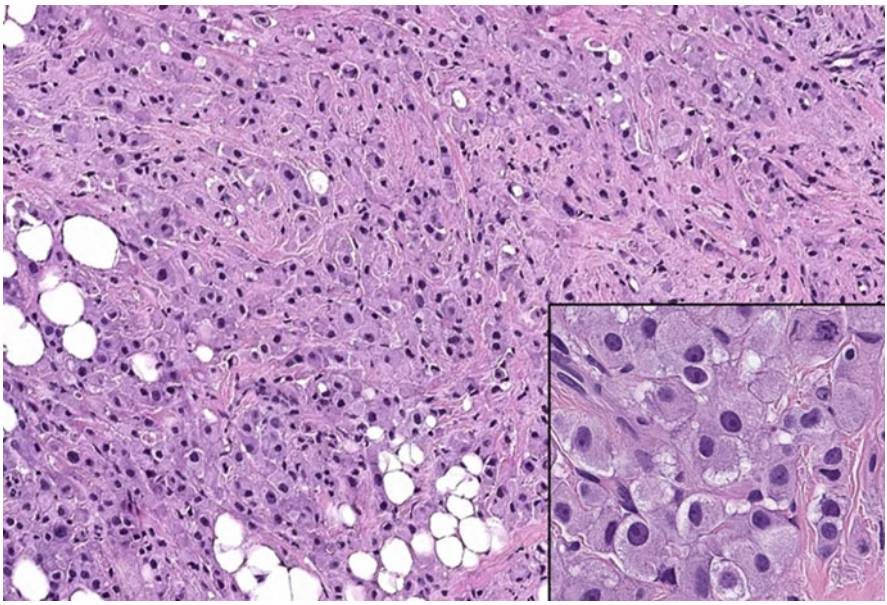

Fig. 11.1 Invasive lobular carcinoma, histiocytoid variant. These tumors are morphologically characterized by sheets/cords of cells with abundant granular cytoplasm and variably eccentric nuclei. Among the possible differential diagnoses of histiocytoid lobular carcinoma, it is worth mentioning some non-neoplastic conditions, such as reactive histiocytic infiltrates and fat necrosis. Hematoxylin and eosin, original magnification 100×; inset 400×. Note. Personal archive

tumor staging, and nodal status are important prognostic factors also in patients with ILC. Moreover, a high Ki67 proliferation index was found to be associated with a high risk of early and late recurrence [19, 20].

In addition to traditional prognostic and predictive factors, other actional biomarkers, such as tumor-infiltrating lymphocytes (TILs) and PD-L1 expression, have been recently included in the pathological characterization of IBC. PD-L1 expression in ILC has been observed both on lymphocyte and tumor cells. Overall, the level of TILs and PD-L1 reported in ILCs are lower than those observed in IDC and with different patterns, suggesting that ILC may be associated with a distinct immune microenvironment [21–24].

As mentioned above, most ILCs are currently classified as HER-2 negative. According to the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP), the HER2 test positivity is defined by protein overexpression (score 3+) at immunohistochemistry (IHC) and/or HER2 score 2+ with gene amplification at in situ hybridization (ISH), while score 2+/ISH negative, score 1+ and score 0 were considered negative [25]. However, the introduction of novel anti-HER2 antibody-drug conjugates requires an in-depth categorization of this "HER2-negative" group, distinguishing tumors with no HER2 expression by IHC (or in less than 10% of tumor cells; score 0) from those with low HER2

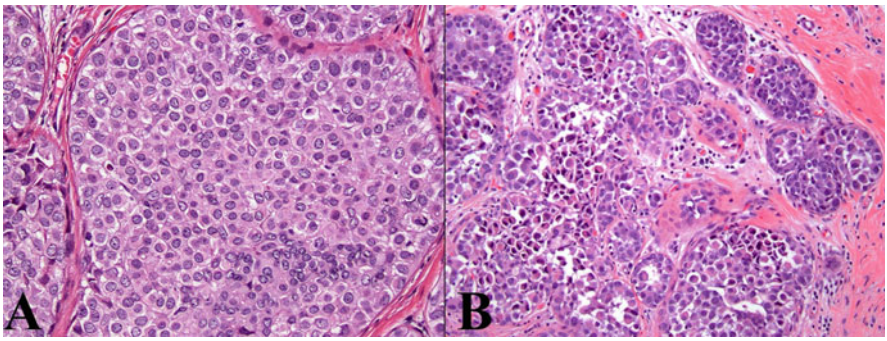

Fig. 11.2 Histological features of lobular carcinoma in situ (LCIS). (**a**) Monomorphic proliferation of polygonal discohesive cells with clear cytoplasm that distend the acini with the maintenance of the lobular architecture. (**b**) Non-invasive lesion with lobular phenotype, showing eccentric large pleomorphic nuclei, conspicuous nucleoli and large eosinophilic granular cytoplasm, consistent pleomorphic lobular carcinoma in situ. Hematoxylin and eosin, original magnification 200×. Adapted from: Guerini-Rocco and Fusco. Premalignant and preinvasive lesions of the breast. In: Breast Cancer: Innovations in Research and Management. Veronesi U, Goldhirsh A, Veronesi P, et al., editors. Springer International Publishing; 2017. p. 103–20 [33]

expression (HER2-low IBC) showing immunohistochemistry HER2 score 1+ or 2+/ISH- [26–28]. Considering ILC, fewer cases have been observed among HER2-low IBC compared to HER2-zero tumors [29, 30].

Non-invasive lobular neoplasia, including lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), are frequently seen in combination with ILC [31–34]. ALH and LCIS are considered risk indicators and non-obligate precursors of invasive breast cancer [35, 36]. The neoplastic cells of ALH/LCIS morphologically resemble those of ILC distending the acini with the maintenance of the lobular architecture. Moreover, akin to the invasive counterpart, these types of non-invasive lobular neoplasia lack E-cadherin expression, confirming the early oncogenicity of *CDH1* alterations in hereditary and non-hereditary lobular breast cancer [35–37] (Fig. 11.2).

11.3 *CDH1* Aberrations: The Hallmark of Lobular Breast Cancer

The *CDH1* gene (16q22.1) encodes for the E-cadherin protein, which is responsible for cell adhesion and suppresses cell motility and invasion [38, 39]. The rationale for the use of E-cadherin as a biomarker in ILC is related to its very biology. This protein has an extracellular domain responsible for cell-to-cell adhesion via homodimerization with other E-cadherin molecules on adjacent cells [40]. The intracellular domain interacts with the actin cytoskeleton indirectly, through a complex formed by several mediators such as α-, β-, and p120-catenins. Therefore, the presence and functionality of E-cadherin are crucial not only in maintaining

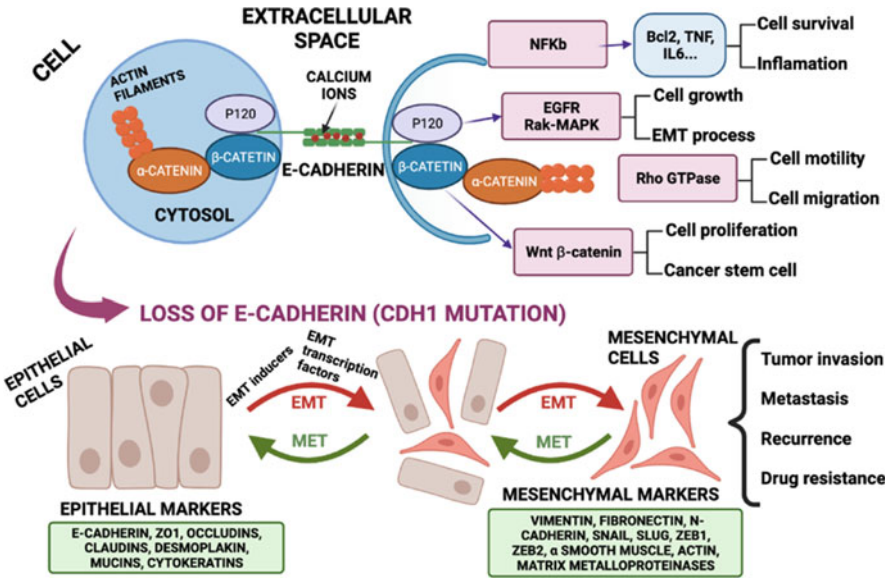

Fig. 11.3 Molecular events mediated by loss of E-cadherin in hereditary lobular carcinoma. E-cadherin is a 120 kDa glycoprotein encoded by the CDH1 gene, located on chromosome 16q22.1, and belongs to the classical Cadherin subgroup. It has an extracellular domain formed by five extracellular ~100 amino acid residue motifs, termed extracellular cadherin repeats. The calcium binding sites are located in the pockets between the repeats. This extracellular domain is mainly responsible for cell-to-cell adhesion via homodimerization with other E-cadherin molecules present on adjacent cells. E-cadherin has a single transmembrane domain that links the extracellular domain with the smaller intracellular domain. The intracellular domain interacts with the actin cytoskeleton indirectly, through a complex formed by several mediators such as α-, β-, and p120-catenins. Therefore, the presence and functionality of E-cadherin are crucial not only in maintaining cell-to-cell adhesion but through the interaction with these mediators, which plays also a role in a variety of intracellular pathways

cell-to-cell adhesion but through the interaction with these mediators, in different intracellular pathways [40, 41] (Fig. 11.3).

The loss of E-cadherin functionality caused by *CDH1* mutations results in the facilitation of epithelial-to-mesenchymal transition and tumorigenesis [42]. This molecular aberration is directly reflected by the non-to-poorly cohesive morphological appearance of lobular carcinoma cells and by the loss of immunohistochemical expression of E-cadherin and cytoplasmic expression of p120-catenins [43]. However, up to 15% of ILC may show E-cadherin expression and abnormal E-cadherin immunoreactivity has been seen in other breast cancer subtypes, including total absence or diminished membrane staining, and punctate or cytoplasmic expression [44, 45] (Fig. 11.4).

In the TCGA series, *CDH1* genomic aberrations have been detected in nearly 12% of all breast cancers including truncating, missense and splice-site mutations, copy number, and structural variants. Somatic *CDH1* mutations have been reported

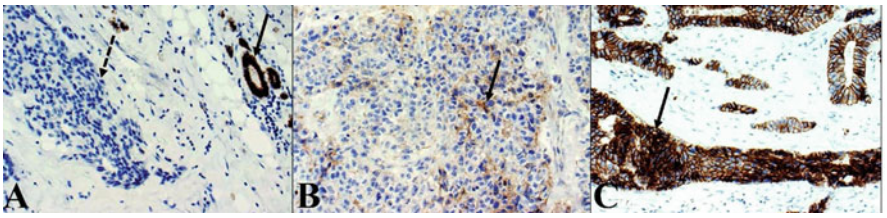

Fig. 11.4 Spectrum of E-cadherin immunoreactivity in breast cancer. Representative micrographs of (**a**) lobular carcinoma showing loss of E-cadherin immunohistochemical expression (dashed arrow) and adjacent normal terminal duct-lobular units with strong membranous E-cadherin staining (full arrow); invasive breast cancers of no special type showing partial loss (**b**) and strong (**c**) membranous immunoreactivity for E-cadherin. E-cadherin immunohistochemistry, original magnification 200×. Adapted from: Corso G, Figueiredo J, De Angelis SP, et al. E-cadherin deregulation in breast cancer. J Cell Mol Med 2020;24:5930–6 [50]

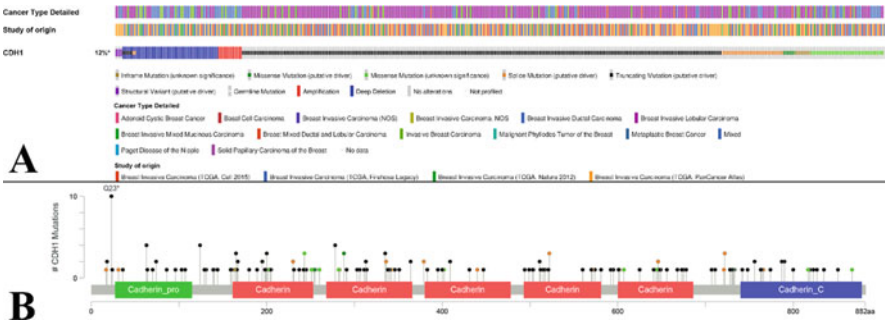

Fig. 11.5 Distribution of *CDH1* mutations in breast cancer. (**a**) Oncoprint visualization of the *CDH1* mutations across different histological subtypes of breast cancer. (**b**) Lollipop plot presenting frequencies and types of *CDH1* mutations. TGCA Combined Study (3835 samples) from https://www.cbioportal.org/, accessed 20th July 2022)

in 50–80% of lobular breast cancer [2, 3, 6] (Fig. 11.5). These mutations mostly co-occur with heterozygous loss of 16q and they are frequently associated with downregulation of CDH1 transcript and protein levels [46]. Interestingly, the complete loss of CDH1 expression alone is not sufficient for invasive carcinoma development, as demonstrated in transgenic animal models. Indeed, other genetic alterations, such as Smad4 and p53, are required to promote invasiveness and metastasis [47–49]. Besides alterations affecting the *CDH1* gene, epigenetic modifications and upregulation of transcriptional inhibitors have also been described as mechanisms of E-cadherin inactivation [50]. An important and frequent epigenetic modification is hypermethylation of the CDH1 promoter. This alteration has been studied in hereditary and non-hereditary lobular breast cancers, which suggests epigenetic silencing as an alternative CDH1 downregulation mechanism. *CDH1* DNA hypermethylation has been demonstrated to be inversely proportional to E-cadherin levels in tumor cells [51].

Interestingly, it has been observed that *CDH1* promoter hypermethylation is associated with reduced HR expression, increased disease progression, a higher metastatic rate, and a more aggressive clinical course overall. It is more frequent in patients presenting with sentinel lymph node metastases at diagnosis and is correlated with disease progression to distant metastases [52, 53]. This has led to the proposal of *CDH1* hypermethylation as a prognostic biomarker to predict poorer outcomes [54]. Another mechanism of E-cadherin inactivation is represented by the overexpression of its transcriptional inhibitors, namely Snail, SLUG, zinc finger E-box-binding (ZEB1 and 2), and TWIST transcription factors [55]. Among these molecules, the one with the highest affinity for the *CDH1* promoter is Snail, which acts by recruiting the mSin3A/Histone Deacetylase1 and 2 (HDAC1/2). Subsequent deacetylation of histones H3 and H4 results in silencing of the gene, thus effectively inhibiting E-cadherin synthesis [56, 57]. ZEB1 and ZEB2 behave similarly to Snail in suppressing *CDH1* transcription, but their mechanisms of action appear to be independent. Thus, it has been hypothesized that at least two transcriptional downregulation complexes of E-cadherin do exist, but whether they participate in tumorigenesis within the same cell remains to be established [58]. High levels of ZEB1 have been found in aggressive BCs and associated with advanced-stage and lymph node metastases. Therefore, ZEB1 has been proposed as an additional prognostic biomarker in breast cancers, in particular in lobular breast cancer [41, 50, 59–61].

E-cadherin and many RTKs tend to co-localize at the basolateral portion of the cell membrane. In particular, the complex formed by the E-cadherin intracellular domain and EGFR has been extensively studied to be involved in adhesion-dependent bidirectional crosstalk. On one hand, cell-to-cell adhesion via E-cadherin inhibits the EGFR signaling pathway, including downstream mediators such as MAPK/ERK with downregulation of cell cycle progression and cellular proliferation [62]. Conversely, it has been demonstrated that cell adhesion transiently activates the EGFR/MAPK signaling cascade, and has a role in tissue growth [63]. Moreover, the upregulation of several RTKs pathways is known to inhibit E-cadherin-dependent cell-to-cell adhesion and promote epithelial-to-mesenchymal transition (EMT), suggesting that E-cadherin plays a role in tumorigenesis even when not directly affected by inactivating mutations [64]. E-cadherin is also known to form a complex with β-catenin. The E-cadherin/ β-catenin complex is crucial in maintaining not only cell-to-cell adhesion but also tissue's architectural homeostasis. Beta-catenin is well known for being a central component of the WNT signal transduction pathway. It has been demonstrated that when catenin is bound by E-cadherin, the result is the promotion of tissue stasis by inhibition of cell proliferation and architectural stabilization. The disruption of the cadherin-catenin complex causes an increase of cytoplasmic un-bound β-catenin. This alters the WNT signaling pathway shifting the balance toward cell growth and proliferation. This effect has been demonstrated to be unrelated to E-cadherin adhesive properties and to be entirely dependent on its β-catenin binding region. In addition, β-catenin has an inhibitory effect on PTEN, a well-known tumor suppressor gene, further promoting uncontrolled cell proliferation [65, 66]. Another signaling pathway influenced by the

interaction between E-cadherin and catenins at the cell membrane is that of the Rho GTPases. The Rho GTPases are a family of proteins involved in the interaction of E-cadherin with the cytoskeleton, a process influenced also by p120-catenin. They promote and regulate the organization of the cytoskeletal network during the formation of adherens junctions. The two Rho GTPase subfamilies most known for being influenced by E-cadherin are Rac and Rho. In normal conditions, E-cadherin activates Rac1 and inhibits Rho through the interaction of p120, increasing cell adhesion and cellular structural stability. Loss of E-cadherin causes an increase in unbound p120, which in turn creates an inversion of this balance. This not only promotes loss of cell-to-cell adhesion by disruption of the adherens junctions but also enhances cellular motility and migration due to rearrangement of the cytoskeletal network. Therefore, the Rho GTPase family has an important role in the process of EMT mediated by E-cadherin loss [67, 68]. Moreover, increased levels of p120 upregulate the NF-kB pathway, which contributes to tumorigenesis by promoting inflammation, cell proliferation, and apoptosis escape [69]. During EMT, when cells have detached from their tissue of origin they start to migrate within the extracellular matrix. E-cadherin loss has been demonstrated to enhance cellular motility in this new environment by upregulation of secretion and activity of metalloproteinases (MMP) [70]. These molecules play a role in matrix digestion and remodeling and, when their activity is increased, tumor cell migration is facilitated. In addition, MMPs have been shown to inactivate E-cadherin by cleavage of its extracellular domain, further demonstrating the close interplay of these two effectors in tumor spread [71]. Besides the loss of cell-to-cell adhesion and EMT, E-cadherin loss also increases the resistance of cells to apoptotic stimuli. This effect is mediated by the inverse relationship between E-cadherin expression and the Notch pathway. Reduction in E-cadherin levels is correlated with upregulation of this pathway, leading to an increase in intracellular levels of Bcl-2. The Bcl-2 family of proteins is known to be involved in the regulation of programmed cell death. Specifically, they have an anti-apoptotic role, thus their upregulation following E-cadherin loss promotes tumor resistance to apoptotic stimuli and improves the survival of neoplastic cells [72]. The interplay between E-cadherin and a plethora of intracellular signaling pathways demonstrates how the role of this molecule in tumorigenesis goes well beyond the loss of cell-to-cell adhesion. This also highlighted the need for detailed characterization and reporting of *CDH1* variants identified, especially at the germline level.

11.4 The Genomic Landscape of Lobular Breast Cancer

During the last decades, broad genomic profiling with high-throughput next-generation sequencing technologies has shown that breast cancers are highly heterogeneous at the molecular level harboring few recurrent genomic aberrations and potentially actionable drivers [2, 4, 5, 73–77]. Overall, *PIK3CA* and *TP53* are the most frequently mutated genes with different mutation rates based on breast cancer subtype. Nearly 40% of estrogen receptor-positive/luminal breast cancer harbor

somatic driver mutations in the *PIK3CA* gene. *TP53* mutations can be detected in 20–30% of luminal tumors but nearly 85% of basal-like/triple-negative breast cancers. Indeed, these triple-negative tumors show also high genomic instability and DNA repair gene aberrations, including *BRCA1/2* alterations [75, 77]. ILC represents a special breast cancer type also at the genomic level. As mentioned above, ILC is characterized by a higher rate of *CDH1* mutations as compared to IDC (63% versus 2% in the TCGA study). Other recurrently mutated genes (reported rate > 2%) in ILC included: *PIK3CA, TBX3, RUNX1, FOXA1, ERBB2, ERBB3, PTEN, MAP3K1, AKT1, ARID1A,* and *TP53*. Besides *CDH1* heterozygous deletion (16q loss) detected in more than 90% of the cases, other recurrent copy number variations involve gain of *CCND1, FGFR1,* and *MYC* genes. Although amplification of the HER2 gene is not frequently seen in ILC, somatic mutations of *ERBB2* have been reported in 2%–15% of cases [2–6, 8, 9, 78]. Overall, as compared to estrogen receptor-positive luminal breast cancer, invasive lobular carcinoma is enriched for *CDH1* mutations and loss, mutation of *TBX3* and *FOXA1*, mutation, and loss of PTEN with activation of AKT pathway but low mutation rate of *GATA-3* [3] (Fig. 11.6).

Triple-negative (hormone receptors-negative and HER2-negative) ILC is a rare disease accounting for nearly 1% of triple-negative breast cancers and it has a poor prognosis. Although no significant differences in gene mutation frequency have been found compared to hormone receptor-positive/her2-negative cases, enrichment for alterations in ErbB and androgen receptor signaling pathways were observed in triple-negative ILC. Moreover, these tumors show a genomic profile distinct from triple-negative IDCs, including higher frequencies of *CDH1*, *ERBB2*, *PI3KCA*, and *FOXA1* mutations [8, 79, 80].

Considering primary and metastatic ILC, similar repertoires of genomic alterations have been described. However, in the metastatic setting higher frequencies of *TP53*, *ESR1*, *NF1,* and *ERRB2* alterations have been reported. Indeed, these genomic alterations may represent mechanisms of endocrine therapy resistance. Moreover, a higher tumor mutational burden has been observed in metastatic ILC as compared to primary tumors [81].

11.5 Conclusion

Lobular breast cancers display peculiar characteristics including morphologic, phenotypic, and transcriptomic features, genomic aberrations, immune microenvironment composition, and clinical behavior. Given the rarity of and maybe low awareness about hereditary CDH1-related ILC, few studies have been specifically focused on this entity and, so far, similar characteristics have been reported. Dedicated investigations are warranted to elucidate the molecular profiles of ILC that arise in women harboring *CDH1* germline mutations. Indeed, there are numerous questions to be uncovered in the molecular mechanisms driving tumorigenesis and disease progression. A focused characterization of the molecular profile of hereditary CDH1-related ILC may enhance our understanding of these tumors and ultimately

Fig. 11.6 Recurrent genomic alterations in *CDH1*-mutated invasive lobular carcinoma. Oncoprint visualization of the most frequently mutated genes in lobular breast carcinomas harboring somatic *CDH1* mutations. TGCA Firehose Legacy series (99 samples) from https://www.cbioportal.org/, accessed 20th July 2022

might aid in establishing effective prevention, screening, and tailored treatment strategies for women carrying *CDH1* germline mutations.

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