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Germline mutations in cancer predisposition genes in patients with invasive lobular carcinoma of the breast

Author Block: S. Yadav[1], H. LaDuca[2], E. C. Polley[1], C. Hu[1], S. N. Hart[1], J. Na[1], R. Gnanaolivu[1], B. Smith[2], D. E. Goldgar[3], T. Pesaran[2], J. S. Dolinsky[2], F. J. Couch[1];

[1]Mayo Clinic, Rochester, MN, [2]Ambry Genetics Inc., Aliso Viejo, CA, [3]Huntsman Cancer Institute, Salt Lake City, UT.

Abstract:

Background:

Invasive lobular carcinoma (ILC) of the breast accounts for approximately 10-15% of all histologic subtypes of breast cancer. However, apart from germline mutations in *CDH1*, the contributions of mutations in other cancer predisposition genes to ILC are largely unknown.

Methods:

The study population included 3,893 women with ILC of the breast who underwent germline multigene panel testing of cancer predisposition genes at Ambry Genetics from March 2012 to December 2016. The prevalence of predisposition gene mutations in women with ILC was assessed relative to 38,004 women with invasive ductal carcinoma (IDC) who underwent germline multigene panel testing at Ambry Genetics during the same timeframe. Associations between mutations in each gene and risk of ILC were evaluated using reference controls.

Results:

Of the 3,893 women with ILC included in this study, 70.7% were non-Hispanic white, 65.1% had a family history of breast cancer, and 96.4% had estrogen receptor (ER) positive breast cancer. The overall frequency of germline mutations in cancer predisposition genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PTEN, RAD51C, RAD51D* and *TP53*) was 7.8% for women with ILC and 10.7% for women with IDC. Mutations in *CDH1* were significantly more frequent (Odds Ratio (OR)=12.1, p<0.001), whereas mutations in *BRCA1* (OR=0.1; p<0.001) and *PALB2* (OR=0.4; p<0.001) were less frequent in women with ILC, compared to women with IDC. When restricting the analysis to ER positive cases only, significant differences in frequencies of *ATM* (OR=0.6, p=0.03), *BRCA1* (OR=0.3, p<0.001), *CDH1* (OR=7.7, p<0.001) and *PALB2* (OR=0.3, p<0.001) were observed

in ILC compared to IDC. By comparison with gnomAD reference controls, *ATM, BRCA2, CDH1, CHEK2, PALB2* and *PTEN* mutations were significantly associated with an increased risk of ILC and IDC (OR>2), *NBN* mutations were associated with ILC (OR=3.4; p<0.001) but not IDC, and *BRCA1* mutations were not associated with increased risk of ILC. Among 274 women with ILC over the age of 50 without history of any other cancer or a family history of breast or ovarian cancer, 14 (5.1%) were found to carry a mutation in one of the genes evaluated.

Conclusions:

In a large cohort of patients with ILC, the frequencies of germline mutations in cancer predisposition genes were similar between ILC and IDC except for *ATM*, *BRCA1, CDH1* and *PALB2*. Six genes, in addition to *CDH1*, were found to be germline predisposition genes for ILC. A substantial proportion of patients older than 50 with ILC without a family history of breast or ovarian cancer or a personal history of other cancers were found to be mutation carriers. These findings improve our understanding of germline genetic drivers of ILC and suggest that multigene genetic testing should be considered for all ILC patients.

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Author Disclosure Information:

S. Yadav: None. **H. LaDuca:** S; A; Ambry Genetics Inc.. **E.C. Polley:** None. **C. Hu:** None. **S.N. Hart:** None. **J. Na:** None. **R. Gnanaolivu:** None. **B. Smith:** S; A; Ambry Genetics Inc.. **D.E. Goldgar:** None. **T. Pesaran:** S; A; Ambry Genetics Inc. **J.S. Dolinsky:** S; A; Ambry Genetics Inc.. **F.J. Couch:** None.

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ZIP/Postal Code: : 55905

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