Guidelines:
2,900 Character limit including spaces
Current Character Count: 2800 including spaces

Title (255 Character Limit):
PHENOTYPIC EXPRESSION OF *CDH1* GERMLINE MUTATIONS UNSELECTED FOR HEREDITARY DIFFUSE GASTRIC CANCER

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Background:
CDH1 mutations cause hereditary diffuse gastric cancer (HDGC), a syndrome associated with very high risks of stomach and lobular breast cancer (LBC). However, HDGC penetrance estimates have been derived from the analysis of a limited number of families with several members affected with gastric cancer, and some at a very young age. This study aimed to assess cancer phenotype among a group of *CDH1* mutation carriers, independent of the indication for testing.
Methods:
A retrospective study was conducted analyzing all *CDH1* mutation carriers identified at a major commercial genetics laboratory and a large academic center. None had *BRCA1/2* or Lynch-syndrome causing mutations. Clinical phenotypes, including the incidence of gastric and/or breast cancer and mean age at diagnosis, were analyzed for *CDH1* mutation carriers (n=114) and family members for whom cancer history data was available (n=690).
Results:
Among mutation carriers, 77% (n=88) had cancer: 63% (n=55) breast; 33% stomach (n=28). Among breast cancers, 51% (n=29) had LBC and 33% (n=18) ductal breast cancer (DBC). Mean ages at diagnosis were 52.1 for LBC, 47.5 for DBC, and 42.0 for gastric cancer, which are significantly lower than mean ages for the general population (59.5, 63.4 and 69, respectively) (P<.05). While 46% of the families had members with breast and gastric cancer; 38% had breast and other cancers, but no gastric cancers; 10% had gastric and other cancers, but no breast cancer; and 6% had neither breast nor gastric cancers. Overall, the observed incidence of breast cancer in these families stratified by age was significantly higher (P<.05) than expected for the US general population.

Five of the eight African American (AA) mutation carriers shared the same likely pathogenic mutation (p.Asp662Terfs), which was not present among any other ethnic groups and also not reported in gnomAD. All five families presented with a breast cancer-only phenotype.
Conclusions:
This study reports the largest series of *CDH1* mutation carriers to date. As selection was not limited to those meeting clinical criteria for HDGC, a new phenotypic spectrum has emerged. The majority of carriers had breast cancers that not only included LBC but also DBC, and nearly half of the families reported no gastric cancer. The high incidence of DBC as well as the young

age at diagnosis in this group suggests an association of *CDH1* mutations with DBC. The recurrent mutation in five AA families could represent a founder mutation for this ethnicity and it could be linked to breast cancer development only. Thus, it will be crucial to determine if specific *CDH1* mutations or other genetic and/or environmental factors associate with distinct phenotypes to potentially adjust cancer prevention strategies based on mutation-specific risk