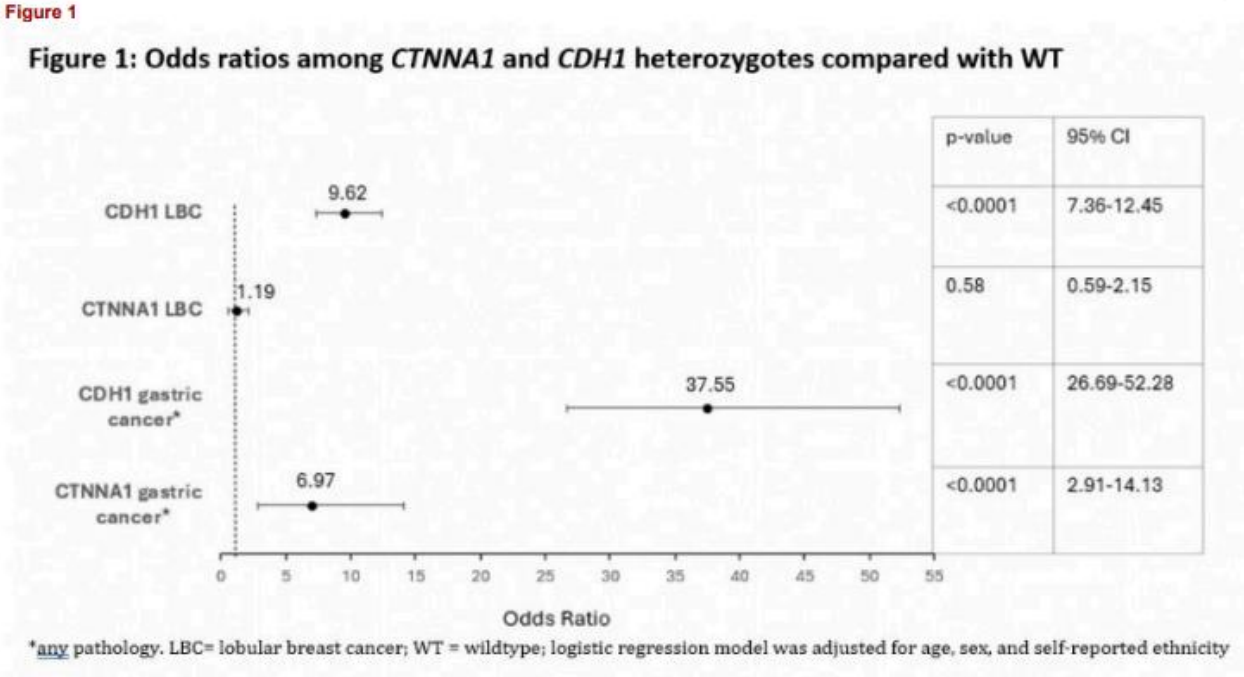
Gastric and lobular breast cancer prevalence in *CTNNA1* heterozygotes identified via multigene panel testing

Jennifer Herrera Mullar, Carolyn Horton, John Ranola, Cassidy Carraway, Linda Polfus, Marcy E Richardson, Rachid Karam
Ambry Genetics

BACKGROUND:Premature truncating variants (PTV) in *CTNNA1* have been implicated in hereditary diffuse gastric cancer (HDGC). Published data reports consist mainly of individuals ascertained for HDGC, which may overestimate penetrance values.
METHODS:Clinical data from individuals with *CTNNA1* PTVs identified via multigene panel testing (MGPT, up to 91 genes) at a diagnostic laboratory were reviewed and compared to individuals with pathogenic or likely pathogenic variants (LP/PV) in *CDH1* and to a wild-type (WT) group. The *CDH1* and *CTNNA1* groups included individuals identified via MGPT from April 2012-December 2023 with no LP/PV in any other autosomal dominant cancer predisposition gene. The WT group (n=37,428) underwent MGPT (March 2019-April 2020) with no P/LPVs. Gastric cancer and lobular breast cancer (LBC) frequencies among *CTNNA1* and *CDH1* heterozygotes were compared to WT using logistic regression.
RESULTS:We identified 270 individuals with *CTNNA1* PTVs, 7 (2.6%) of whom reported gastric cancer, and 10 (3.7%) with LBC. We identified 414 individuals with *CDH1* LP/P, 66 (15.9%) of whom reported gastric cancer, and 81 (19.6%) with LBC. Compared to WT, *CTNNA1* heterozygotes were 7.0-fold more likely to be diagnosed with gastric cancer (OR 7.0; 95% CI [2.9-14.1];p-val 1.03 x 10-6), and *CDH1* heterozygotes were 37.5-fold more likely to be diagnosed with gastric cancer (OR 37.5; 95% CI [26.7-52.3];p-val <2x10-16). *CTNNA1* heterozygotes had no significant increase in LBC relative to WT (OR 1.2; 95% CI [0.59-2.15];p-val: 0.58), in contrast with *CDH1* heterozygotes (OR 9.6; 95% CI [7.4-12.5]; p-val: <2x10-16).
CONCLUSIONS:This genotype-first series supports that *CTNNA1* PTVs are associated with gastric cancer, but with dramatically reduced gastric cancer risks compared to *CDH1* heterozygotes, and that LBC may not be part of the tumor spectrum in *CTNNA1* PTV heterozygotes. Based on these findings, it is imperative that *CTNNA1*-specific guidelines be developed for the clinical management of patients identified with PTVs in *CTNNA1*.

Keywords: hereditary diffuse gastric cancer, CDH1, CTNNA1, genetic counseling, low penetrance cancer predisposition

Figure 1



Odds ratios among {CTNNA1} and {CDH1} heterozygotes compared with WT

Table 1

Table 1: Cohort characteristics

CTNNA1 PTV Cohort	N (%)	*CDH1* LP/P Cohort	N (%)	MGPT-WT Cohort	N (%)
Sex		**Sex**		**Sex**	
Female	236 (87.41%)	Female	323 (78.02%)	Female	32275 (86.67%)
Male	33 (12.22%)	Male	79 (19.08%)	Male	5009 (13.45%)
Unknown	1 (0.37%)	Unknown	12 (2.90%)	Unknown	2 (0.01%)
Ethnicity		**Ethnicity**		**Ethnicity**	
Black/African American	23 (8.52%)	Black/African American	32 (7.73%)	Black/African American	2740 (7.36%)
Ashkenazi Jewish	21 (7.78%)	Ashkenazi Jewish	12 (2.90%)	Ashkenazi Jewish	1756 (4.71%)
Asian	7 (2.59%)	Asian	10 (2.42%)	Asian	1364 (3.66%)
White	145 (53.70%)	White	266 (64.25%)	White	23625 (63.43%)
Hispanic	12 (4.44%)	Hispanic	29 (7.00%)	Hispanic	2140 (5.75%)
Mixed Ethnicity	5 (1.85%)	Mixed Ethnicity	10 (2.42%)	Middle Eastern	249 (0.67%)
Native American	1 (0.37%)	Middle Eastern	7 (1.69%)	Mixed Ethnicity	1338 (3.59%)
Other/Unknown	55 (20.34%)	Other/Unknown	4 (0.97%)	Native American	38 (0.10%)
				Other/Unknown	4036 (10.84%)
Gastric Cancer		**Gastric Cancer**		**Gastric Cancer**	
Yes	7 (2.59%)	Yes	66 (15.94%)	Yes	159 (0.43%)
No/not reported	264 (97.78%)	No/not reported	348 (84.06%)	No/not reported	37089 (99.57%)
LBC		**LBC**		**LBC**	
Yes	10 (3.70%)	Yes	81 (19.57%)	Yes	1210 (3.25%)
No/not reported	261 (96.67%)	No/not reported	333 (80.43%)	No/note reported	36038 (96.75%)

LP = likely pathogenic variant; P = pathogenic variant; WT = wildtype (no mutations identified in any gene); LBC = lobular breast cancer

Cohort characteristics