Clinical Characterization of Patients with Germline *CTNNA1* and *CDH1* Mutations

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Background

- Pathogenic variants (PVs) and likely PVs (LPVs) in *CDH1* cause hereditary diffuse gastric cancer (HDGC) syndrome.
- More recently, germline *CTNNA1* PV/LPVs have been identified in families meeting HGDC testing criteria.
- In individuals up to 80 years of age, the estimated risks of diffuse gastric cancer in carriers of *CDH1* PV/LPVs or *CTNNA1* PV/LPVs are up to 83% and 57%, respectively.[1-4]
- In female carriers of *CDH1* PV/LPVs up to 80 years of age, the estimated lobular breast cancer (LBC) risk is up to 52%. However, the association between carrying a *CTNNA1* PV/LPV and LBC risk is currently unknown.[1]
- **Objective:** Characterize *CTNNA1* and *CDH1* PV/LPV rates, co-occurring mutations, and cancer history in patients tested with a hereditary cancer panel through a single commercial diagnostic laboratory.

Methods

- Patients who were clinically tested with a multi-gene hereditary cancer panel with PV/LPVs in *CDH1* (tested between September 2013 and August 2023) or *CTNNA1* (tested between August 2022 and August 2023) were identified.
  - Individuals were excluded from the analysis if they 1) had undergone targeted testing for PV/LPVs previously identified in family members, or 2) had suspected mosaic findings (variant allele frequency <30%).
- The clinical information, including patient sex, was obtained from test request forms submitted by healthcare providers at the time of testing.

Conclusions

- Although gastric cancer and LBC were noted in the clinical history of 2 separate carriers of *CTNNA1* PV/LPVs, our cohort reported a lower incidence of these cancers in *CTNNA1* carriers as compared to *CDH1* carriers.
- Our data suggest that *CTNNA1* may be a lower penetrance gene within the HGDC spectrum. However, additional research is necessary to elucidate cancer risk.

References

1. Kaurah P et al., GeneReviews. Updated 2018. 2. van der Post RS et al. *J Med Genet* .2015. 52(6):361-74. 3. Hansford S et al. *JAMA Oncol*. 2015. Apr;1(1):23-32. 4. Coudert M et al. *J Med Genet*. 2022. 59(12):1189-1195.

Results

Table 1: Carriers of *CTNNA1* or *CDH1* PV/LPVs and Co-Occurring Mutations

	Carriers of *CTNNA1* PV/LPVs N (%)	Carriers of *CDH1* PV/LPVs N (%)
Total Patients	49 (100.0%)	549 (100.0%)
Female	43 (87.8%)	496 (90.3%)
Male	6 (12.2%)	53 (9.7%)
Average Age	52.3 years	50.3 years
Co-Occurring *CTNNA1* and *CDH1* Mutations		
CTTNA1	---	0 (0.0%)
CDH1	0 (0.0)	---
Other Co-Occurring Mutations		
CHEK2	0 (0.0%)	10 (1.8%)
BRCA2	2 (4.1%)	8 (1.5%)
BRCA1	0 (0.0%)	4 (0.7%)
HOXB13	0 (0.0%)	4 (0.7%)
PMS2	0 (0.0%)	3 (0.5%)
MSH6	0 (0.0%)	2 (0.4%)
PALB2	0 (0.0%)	2 (0.4%)
ATM	1 (2.0%)	1 (0.2%)
BRIP1	0 (0.0%)	1 (0.2%)
CHEK2 & MSH2	0 (0.0%)	1 (0.2%)
MSH2	1 (2.0%)	0 (0.0%)
SDHA	1 (2.0%)	0 (0.0%)

Figure 1: Percent of Carriers of *CTNNA1* or *CDH1* PV/LPVs with Personal or Family Cancer Histories

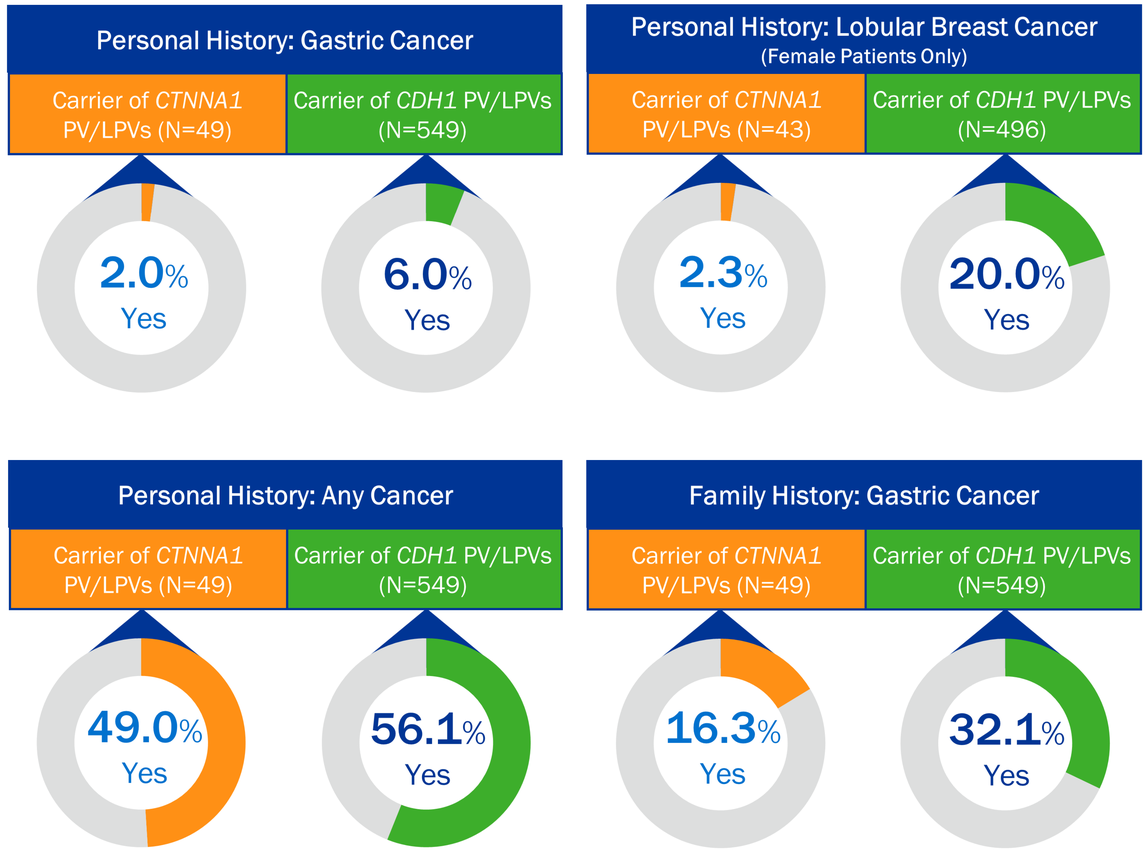

Figure 2: Gene Map of the Observed *CTNNA1* PV/LPVs