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. 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 CDH1 PV/LPV and LBC risk is currently unknown. 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