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

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Premature truncating variants (PTV) in *CTNNA1* have been implicated in hereditary diffuse gastric cancer (HDGC). Published data thus far reports individuals ascertained for HDGC, which may overestimate penetrance values. Clinical data from individuals with a PTV in *CTNNA1* identified via pan-cancer hereditary cancer multigene panel testing (MGPT, up to 91 genes) at a single diagnostic laboratory were reviewed and compared to individuals with a pathogenic or likely pathogenic variant (P/LPV) 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 comparison group of 37,428 individuals underwent pan-cancer MGPT (March 2019-April 2020) and had no P/LPVs detected. Demographic and clinical information were provided by the ordering clinician. Gastric cancer and lobular breast cancer (LBC) frequencies among *CTNNA1* and *CDH1* heterozygotes were compared to WT cases using logistic regression, adjusted for age and sex. We identified 270 individuals with a PTV in *CTNNA1*. Seven (2.6%) reported a personal history of gastric cancer, and 10 (3.7%) reported a personal history of LBC. We identified 414 individuals with a P/LPV in *CDH1*, 66 (15.9%) of whom reported a personal history of gastric cancer, and 81 (19.6%) with a personal history of LBC. Compared to the WT cohort, *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 1.03×10^{-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 $<2\times10^{-16}$). *CTNNA1* heterozygotes had no significant increase in the prevalence of 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: $<2\times10^{-16}$). Our analyses represent the largest series of *CTNNA1* heterozygotes ascertained via MGPT for diverse cancer indications. Compared to HDGC cohorts, our approach reduces enrichment for gastric and lobular breast cancer and provides a less-biased estimation of cancer risk. These results indicate that while PTVs in *CTNNA1* are associated with gastric cancer, the risk is dramatically lower than in *CDH1* heterozygotes. Our analysis suggests that lobular breast cancer is not part of the tumor spectrum in *CTNNA1* PTV heterozygotes; however, additional studies are needed to confirm this finding. This genotype-first series supports that *CTNNA1* is a low penetrance gastric cancer predisposition gene, with significantly increased risk over WT individuals but substantially reduced gastric cancer risks compared to *CDH1* 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*.