Breast cancer prevalence in *CTNNA1* heterozygotes identified via hereditary cancer multigene panel testing

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BACKGROUND

- *CTNNA1*-related hereditary diffuse gastric and lobular breast cancer (DGLBC; MONDO:0100256) is a newly described cancer predisposition condition.
- *CTNNA1* variants have primarily been described in families ascertained for suspicion of HDGC.[1, 2, 3]
- *CTNNA1* variants have been detected in individuals with breast cancer (primarily unspecified breast cancer); the lobular breast cancer phenotype has been rarely reported.[3, 4]
- A clinically relevant association between *CTNNA1* and breast cancer (lobular or unspecified breast cancer) has not been demonstrated.

METHODS

Retrospective review of clinical data from individuals with multi-gene panel testing (**MGPT**) results 2012-2023 (up to 85 genes)

Individuals with (likely) pathogenic variants in any other cancer predisposition genes excluded

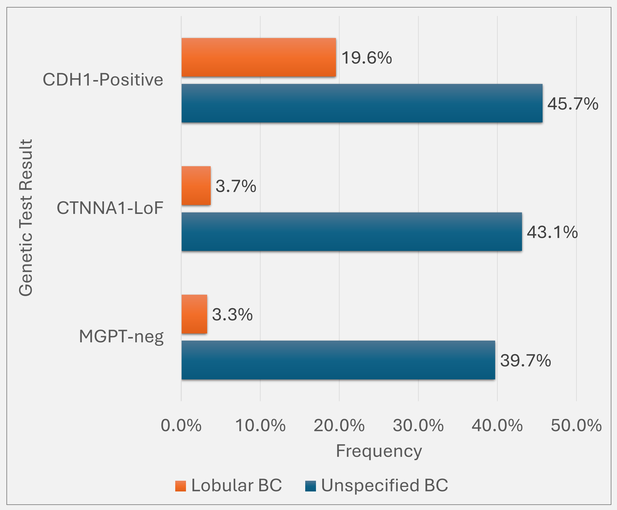
- Study cohort: *CTNNA1* Loss-of-Function (**LOF**) variants (n=270)
- Positive controls: *CDH1* (likely) pathogenic variants (n=414)
- Negative controls: MGPT-negative (76 genes, n=37,428)

Comparison of LBC, UBC, DGC, and UGC frequencies among *CTNNA1* and *CDH1* heterozygotes relative to MGPT-negatives using logistic regression, adjusted for age and sex

RESULTS

FIG 1: Frequency of breast and gastric cancer among *CDH1* and *CTNNA1* heterozygotes compared to MGPT-negative individuals

A: Breast Cancer



B: Gastric Cancer

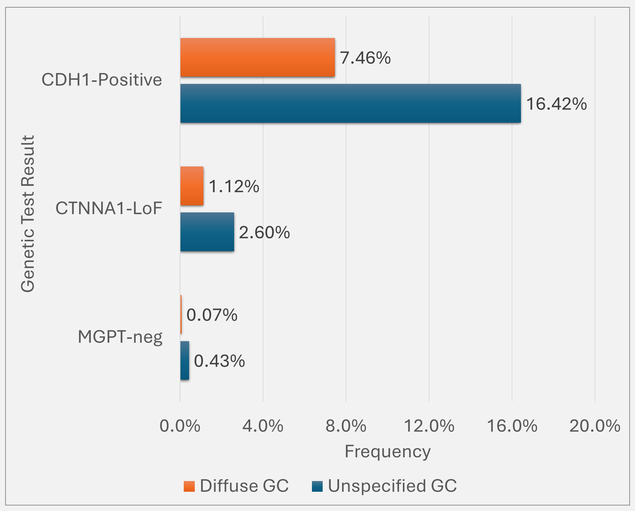
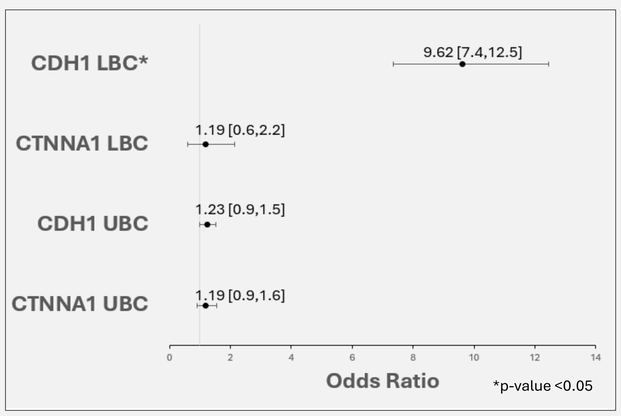
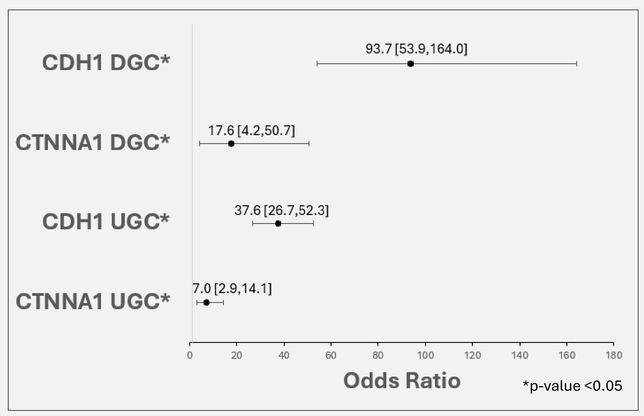


FIG 2: Odds ratios among *CDH1* and *CTNNA1* heterozygotes compared to MGPT-negative individuals

A: Lobular breast cancer (LBC) and Unspecified breast cancer (UBC)



B: Diffuse gastric cancer (DGC) and Unspecified gastric cancer (UGC)



TAKE HOME POINTS

- **This is the largest series examining cancer associations in *CTNNA1* heterozygotes, allowing for analyses with sufficient power (82% power to detect an OR of 1.6 given our cohort size) to detect such associations.**
- ***CTNNA1* loss-of-function variants did not show an association with breast cancer (lobular or unspecified), suggesting breast cancer is not part of thxe cancer spectrum (FIG 1A, 2A).**
- ***CTNNA1* loss-of-function variants showed an association with gastric cancer, but odds was much lower than for *CDH1* (over 5-fold lower OR) (FIG 1B, 2B).**
- **These data indicate cancer risks distinct from *CDH1* and as such, warrant distinct clinical management guidelines for *CTNNA1* heterozygotes.**

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