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; however, the association with LBC has not been established. We compared the prevalence of BC (LBC and unspecified) in *CTNNA1* heterozygotes to *CDH1*-positive (known LBC association) and negative multigene panel testing (MGPT) cohorts.

Methods: Clinical data from individuals undergoing hereditary cancer MGPT (up to 85 genes) at a diagnostic laboratory (April 2012-December 2023) were reviewed. BC frequencies were analyzed in individuals with premature truncation variants (PTV) in *CTNNA1* (n=270) or *CDH1 (*n=414*)* and individuals with negative MGPT (n=37,428). Individuals with a likely pathogenic or pathogenic variant (LP/P) in another cancer predisposition gene were excluded. LBC and unspecified BC frequencies among *CTNNA1* and *CDH1* heterozygotes were compared with MGPT-negative (wildtype, WT) probands using logistic regression.

Results: The prevalence of unspecified BC in the *CTNNA1, CDH1*, and WT cohorts was 43.1% (n=116), 45.7% (n=189), and 39.7% (n=14,733), respectively. Compared to WT, there was no significant association of unspecified BC in *CTNNA1* heterozygotes (OR 1.19; 95% CI [0.92-1.55]; p-value 0.18) or *CDH1* heterozygotes (OR 1.23; 95% CI [0.98-1.53]; p-value 0.07). The prevalence of LBC in the *CTNNA1, CDH1*, and WT cohorts was 3.70% (n=10), 19.57% (n=81), and 3.25% (n=1,210), respectively. There was no significant association of LBC in *CTNNA1* heterozygotes compared to WT (OR 1.19; 95% CI [0.59-2.15]; p-value 0.58), in contrast to *CDH1* heterozygotes (OR 9.62; 905% CI [7.36-12.45; p-value<0.0001).

Conclusions: This is the largest series comparing BC prevalence in *CTNNA1* heterozygotes to WT and *CDH1*-positive cohorts, allowing for analyses with sufficient power (82% power to detect an OR of 1.6 given our cohort size) to detect such associations. Our analyses show no significant association of LBC or unspecified BC in individuals with PTVs in *CTNNA1*, suggesting that BC may not be part of the cancer spectrum.