Unexpected *CDH1* Mutations Identified on Multigene Panels

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Background: Hereditary Diffuse Gastric Cancer syndrome (HDGC), caused by mutations in the *CDH1* gene, results in approximately 80% risk of diffuse gastric cancer (DGC) and up to a 60% risk of lobular breast cancer. Testing for *CDH1* mutations is recommended in individuals who meet the International Gastric Cancer Linkage Consortium (IGCLC) guidelines: 1) 1 DGC under age 40, or 2) 2 cases of gastric cancer, one confirmed DGC under age 50, or 3) 3 confirmed cases of DGC at any age (all 1° or 2° relatives), or 4) personal or family history of DGC and lobular breast cancer, one diagnosed <50. However, in patients who do not meet IGCLC criteria or do not have phenotypes suggestive of HDGC, *CDH1* targeted testing is not typically performed. Our aim is to describe phenotypes of incidentally found *CDH1* mutation carriers identified through multiplex panel testing and the implications for medical management. **Method:** We conducted a retrospective review of a laboratory based cohort (n=19,218) and a cancer genetics clinic based cohort (n=318) tested by multiplex gene panel analysis to evaluate *CDH1* mutation prevalence and correlation with clinical phenotype. *CDH1* mutation carriers were classified as 1) "IGCLC +" (met criteria), 2) "IGCLC -, partial phenotype" (gastric cancer >40 or lobular breast cancer present but IGCLC criteria not met), 3) "IGCLC -, no phenotype." **Results:** In the laboratory-based subset, 13 of 19,218 (0.07%) patients were identified as having a *CDH1* mutation. Of the 13 cases, 3 were classified as "IGCLC+." Five of 13 were classified as "IGCLC-, partial phenotype" due proband's diagnosis of lobular breast cancer, or in one case, later onset diffuse gastric cancer with no family history suggestive of a *CDH1* mutation. Finally, five cases were classified as "IGCLC-, no phenotype." In the clinic-ascertained cohort, 4 of 318 (1.26%) had a deleterious *CDH1* mutation. One case was classified as "IGCLC+", due to her family history, however, the proband's presentation was atypical as she was diagnosed with invasive ductal (rather than lobular) breast carcinoma <50 years. Two of the 4 patients were "IGCLC-, partial phenotype" as they presented with lobular breast cancer but no family history of gastric cancer. The remaining case was "IGCLC-, no phenotype", because the proband had invasive ductal breast cancer and no family history of gastric or lobular breast cancer. For the clinic-ascertained patients with unexpected deleterious *CDH1* mutations management options consistent with established HDGC guidelines were recommended. In the combined cohort 76.4% (13/17) of identified *CDH1* mutations did not meet IGCLC criteria. **Conclusion:** This case series demonstrates that individuals who carry *CDH1* mutations may not fit the accepted diagnostic paradigm and that multiplex panel testing identified deleterious mutations in individuals who may not have been evaluated by traditional targeted gene testing. The future challenge lies in determining the significance of these unanticipated mutations in regards to pathogenicity, penetrance, and prevalence of *de novo* mutations compared to previously described *CDH1* mutation carriers and then translating this into appropriate clinical management. Additional clinical follow-up and longitudinal prospective analyses will be required to meet these challenges.