A novel missense variant in CDH1 causes hereditary diffuse gastric and lobular breast cancer syndrome independently of splicing

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BACKGROUND: Pathogenic variants (PVs) in CDH1 cause hereditary diffuse gastric and lobular breast cancer syndrome (DGLBC). Most CDH1 PVs described in DGLBC families are expected to cause protein truncation or nonsense mediated decay. Currently, the only consensus missense CDH1 PVs associated with DGLBC disrupt splicing. The absence of non-spliceogenic missense CDH1 PVs suggests that missense changes are generally tolerated; however, rare undiscovered missense PVs may exist. Herein we present clinical, structural, and RNA evidence supporting the CDH1 p.G212V c.635G>T as a likely PV, whose mechanism of pathogenicity is through the impact of the missense change rather than splicing.

METHODS: Retrospective review of clinical and RNA data, when available, was performed for six carriers of this variant and used with structural analysis and literature review for classification.

RESULTS: Families with CDH1 p.G212V c.635G>T fulfilled guidelines for CDH1 testing. The variant segregated with disease, with a total of six carriers between two families. Cancer histories included DGC (ages 25-57) and LBC (age 80). RNA studies did not identify any abnormal splicing in the CDH1 gene. However, structural analysis indicated that the variant is expected to destabilize the structure. A close-match variant, p.G212E, is reported as disease causing in the literature.

CONCLUSIONS: The clinical, structural, and hot-spot data, support the CDH1 p.G212V c.635G>T as likely pathogenic (PS4, PM2_supporting, PP1_supporting, PM1_supporting, PM5). However, it is important to note that this variant would not reach a likely pathogenic classification using the CDH1 variant curation expert panel guidelines, in part because many of the codes used to evaluate missense changes are not currently recommended due to the absence of missense PVs available to evaluate their use. It is expected that the emergence of variants such as this will help to refine these guidelines. I hereby confirm that the consent of the relevant patient(s) has been obtained to submit this abstract.