A novel de novo *CDH1* germline variant aids in the classification of carboxy-terminal E-cadherin alterations predicted to escape nonsense-mediated mRNA decay

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Abstract Most truncating *cadherin 1* (*CDH1*) pathogenic alterations confer an elevated life-time risk of diffuse gastric cancer (DGC) and lobular breast cancer (LBC). However, transcripts containing carboxy-terminal premature stop codons have been demonstrated to escape the nonsense-mediated mRNA decay pathway, and gastric and breast cancer risks associated with these truncations should be carefully evaluated. A female patient underwent multigene panel testing because of a personal history of invasive LBC diagnosed at age 54, which identified the germline *CDH1* nonsense alteration, c.2506G>T (p. Glu836*), in the last exon of the gene. Subsequent parental testing for the alteration was negative and additional short tandem repeat analysis confirmed the familial relationships and the de novo occurrence in the proband. Based on the de novo occurrence, clinical history, and rarity in general population databases, this alteration was classified as a likely pathogenic variant. This is the most carboxy-terminal pathogenic alteration reported to date. Additionally, this alteration contributed to the classification of six other upstream *CDH1* carboxy-terminal truncating variants as pathogenic or likely pathogenic. Identifying the most distal pathogenic alteration provides evidence to classify other carboxy-terminal truncating variants as either pathogenic or benign, a fundamental step to offering presymptomatic screening and prophylactic procedures to the appropriate patients.

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Ontology terms: neoplasm of the breast; neoplasm of the gastrointestinal tract

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CASE PRESENTATION

The *cadherin 1* (*CDH1*) gene (NM_004360.3) encodes E-cadherin, a cellular adhesion protein that acts as a tumor suppressor by inhibiting cell invasion (Kourtidis et al. 2017). Germline mutations in *CDH1* cause hereditary diffuse gastric cancer (HDGC) and lobular breast cancer (LBC) syndrome (OMIM 137215). For carriers of pathogenic alterations, the estimated lifetime risk of developing diffuse gastric cancer (DGC) is up to 70% for men and up to 56% for women (Hansford et al. 2015). Women also have an approximate 42% lifetime risk of LBC (Hansford et al. 2015). A clinical diagnosis of HDGC is established in a proband with confirmed DGC and meeting one of the following criteria: (1) at least one first- or second-degree relative with gastric cancer at any age; (2) a diagnosis of DGC before the age of 40; (3) family history of both DGC and LBC (one diagnosis before the age of 50). Confirmatory genetic testing is suggested. Genetic testing should also be considered for patients with other

HDGC-associated phenotypes, including history of bilateral LBC or family history of at least two LBC cases before the age of 50, patients with history of DGC and cleft lip/palate, and those identified with signet ring cell (SRC) carcinoma precursor lesions by gastric endoscopy (van der Post et al. 2015a).

The majority of germline *CDH1* pathogenic alterations result in premature stop codons (e.g., nonsense, frameshift, canonical ± 1 or 2 splice sites), most of which are predicted to elicit nonsense-mediated decay (NMD), a mRNA quality control pathway that destabilizes abnormal transcripts containing premature stop codons (Karam et al. 2008). NMD is triggered by the translation machinery detecting an exon junction protein complex downstream from a premature stop codon; however, premature stop codons located in close proximity to, or beyond, the last exon–exon junction are predicted to escape NMD (Holbrook et al. 2004; Rivas et al. 2015). This “NMD boundary” is located in the penultimate exon of any transcript, ~ 55 nt upstream of the last exon–exon junction. Premature stop codons located downstream from the boundary are predicted to escape NMD because there is no exon–exon junction complex downstream to be detected by the translation machinery (Holbrook et al. 2004; Karam et al. 2013). This is particularly relevant for variant interpretation, because transcripts containing truncating variants located downstream from the boundary cannot be assumed to undergo degradation by the NMD pathway. For this reason, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) recommends caution and consideration of additional lines of evidence, such as clinical evidence, RNA analysis, and/or structural analysis, when classifying truncating variants predicted to escape NMD (Richards et al. 2015).

With this recommendation in mind, a retrospective review of a diagnostic laboratory cohort of approximately 490,000 sequenced *CDH1* alleles was performed to identify all *CDH1* alterations that resulted in premature stop codons past the NMD boundary ($\sim c.2385/p.795$). A total of 11 carboxy-terminal alterations were identified (Fig. 1A), the most carboxy-terminal pathogenic truncation being *CDH1* c.2506G>T (p.Glu836*). This alteration was identified in an Asian female individual that underwent multigene panel testing (MGPT) because of a personal history of an ER⁺/PR[−]/HER2[−] LBC diagnosed at age 54 (Fig. 1B). Of note, the MGPT also included and was negative for alterations in the following genes: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *EPCAM*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *SMARCA4*, *STK11*, and *TP53*. Family history was not suspicious for HDGC. Subsequent parental testing revealed both parents were negative for the alteration (Fig. 1C), and additional short tandem repeat analysis confirmed the familial relationships and the de novo occurrence in the proband (Fig. 1D). In addition, seven alterations were identified downstream from the *CDH1* NMD boundary but upstream of c.2506G>T (p.Glu836*), as well as three other truncations past amino acid position 836 (Fig. 1A).

TECHNICAL ANALYSIS AND METHODS

A retrospective review of the Ambry Genetics database was performed to identify all *CDH1* variants that resulted in premature stop codons past the NMD boundary. Demographic, clinical history, and cancer family history were collected from test requisition forms, clinic notes, pathology reports, and pedigrees provided by ordering clinicians at the time of testing. All variants underwent assessment and review of available evidence (e.g., population frequency information, published case reports, case/control and functional studies, internal cooccurrence and cosegregation data, evolutionary conservation, and in silico predictions). Variants were further classified following a five-tier variant classification protocol (pathogenic mutation; likely pathogenic [LP]; variant of uncertain significance [VUS]; likely benign [LB]; and benign) which is based on published guidelines by the American College of Medical

Figure 1. Characterization of *CDH1* carboxy-terminal variants. (A) Schematic representation of the E-cadherin protein highlighting the germline alterations identified in the gene's NMD resistant zone. (B) Proband with a personal history of LBC diagnosed at age 54, tested positive for *CDH1* c.2506G>T (p.Glu836*) on MGPT. (C) Sanger sequencing of the proband and her parents confirmed the alteration in the proband and revealed parents were negative. (D) Short tandem repeat analysis confirmed paternity and de novo occurrence of *CDH1* c.2506G>T (p.Glu836*) in the proband.

Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) (Richards et al. 2015; Pesaran et al. 2016). All variants classified by Ambry Genetics are submitted to the ClinVar public database.

All patients were tested between May 2013 and January 2018, and underwent analysis of the *CDH1* gene via multigene panel testing, single-gene analysis, or targeted testing for a familial alteration. All testing at Ambry Genetics was performed by next-generation sequencing analysis or Sanger sequencing, depending on the clinical test ordered. Targeted next-generation sequencing was performed on samples received for multigene panels (Shendure and Ji

2008; Mamanova et al. 2010). Briefly, genomic deoxyribonucleic acid (gDNA) was isolated from the patient's specimen using standardized methodology and quantified. Sequence enrichment was carried out by a bait-capture methodology using long biotinylated oligonucleotide probes followed by polymerase chain reaction (PCR) and next-generation sequencing on HiSeq2500 or NextSeq500 instruments (Illumina). Additional Sanger sequencing was performed for any regions missing or with insufficient read depth coverage for reliable heterozygous variant detection. Reportable small insertions and deletions, potentially homozygous variants, variants in regions complicated by pseudogene interference, and single-nucleotide variant calls not satisfying 100× depth of coverage and 40% het ratio thresholds were verified by Sanger sequencing (Mu et al. 2016). Sanger sequencing was performed on samples received for single-site analysis or full-gene analysis (Sanger et al. 1977; Smith et al. 1986). Briefly, gDNA was isolated from the patient's specimen using standardized methodology, quantified, and amplified with gene-specific primers and bidirectionally sequenced using Big Dye Terminator version 3.1 on an ABI3730xl DNA analyzer (Applied Biosystems). Chromatogram analysis was conducted using Sequence Pilot version 4.2.1 (JSI Medical Systems).

VARIANT INTERPRETATION

Although most *CDH1* variants resulting in truncations upstream of the NMD boundary can be confidently classified as pathogenic, classification of carboxy-terminal truncations that escape NMD are less straightforward, as these transcripts may result in partially functional proteins (Sasaki et al. 2000). In this scenario, the ACMG/AMP guidelines recommend that other lines of evidence be considered, such as the existence of other well-characterized downstream carboxy-terminal truncating pathogenic variants (Richards et al. 2015). To our knowledge, the most carboxy-terminal pathogenic truncation previously described in the literature is c.2430delT (Hansford et al. 2015). Therefore *CDH1* c.2506G>T (p.Glu836*), being downstream from this alteration, could not be assumed to result in loss of function, and interpretation depended on additional evidence. In this specific case, the de novo occurrence proved fundamental to its classification, in addition to the proband's clinical history and the variant's rarity in general population databases (Table 1). Altogether this evidence was sufficient to classify *CDH1* c.2506G>T (p.Glu836*) as a likely pathogenic clinically actionable alteration. According to the National Comprehensive Cancer Network (NCCN) and others (van der Post et al. 2015a), medical management for carriers of clinically actionable *CDH1* alterations (pathogenic/likely pathogenic) includes presymptomatic screening and preventive measures, such as prophylactic gastrectomy and consideration of risk-reducing mastectomy. Because of the high cancer risks and potential for morbidity associated with pathogenic *CDH1* alterations, it is important to correctly identify these alterations and manage at-risk individuals appropriately.

The five carboxy-terminal truncations located upstream of *CDH1* c.2506G>T (p.Glu836*) were c.2398delC (p.Arg800Alafs*16), c.2430delT (p.Phe810Leufs*6), c.2446A>T (p.Lys816*), c.2474dupC (p.Pro826Alafs*3), and c.2490dupG (p.Leu831Alafs*4). They all met the predicted loss of function, phenotype, and rarity ACMG/AMP criteria and were classified as pathogenic or likely pathogenic variants (Table 1). These variants were associated with DGC and/or LBC in our cohort or the literature and were absent in population databases (Table 1). Because these alterations are predicted to result in transcripts that escape NMD, the proposed mechanism for pathogenicity is loss of function due to disruption of the cytoplasmic domain, which includes the catenin-binding domain (Fig. 1A). The catenin-binding domain promotes protein clustering at the adherens junction and stabilizes cell adhesion (Kourtidis et al. 2017). Therefore, truncation of this region of the protein may impair cellular adhesion and promote cell invasion.

Table 1. Summary of evidence for CDH1 carboxy-terminal variants identified in a diagnostic laboratory cohort of approximately 490,000 sequenced CDH1 alleles

Genomic location	HGVs cDNA	HGVs protein	Zygosity	Proband tumor (age)	Family criteria Met (A-F) ^a	Ambry frequency (X/490,000 CDH1 alleles)	Population frequency (gnomAD)	Literature	ACMG/AMP criteria Met ^b	Variant interpretation
Chr 16:68863659 (GRCh37)	NM_004360.3: c.2398delC	p.Arg800Alafs*16	Heterozygous	NP	NP	1/490,000	NA	Kaurah et al. 2007 (Newfoundland founder mutation; four Newfoundland families with DGC/LBC), Petridis et al. 2014 (patient with bilat LCIS and unilateral LBC in 30s), Muir et al. 2016 (two gastric/breast cancer families)	PVS1 PM2 PP4	Pathogenic
Chr 16:68863705-68863708 (GRCh37)	NM_004360.3: c.2430delT	p.Phe810Leufs*6	Heterozygous	1) LCIS 39 2) DGC 68 3) LBC 37 4) IDC 40s	1) D 2) A 3) D 4) None	4/490,000	NA	Hansford et al. 2015 (seen in a patient with DGC at 45 and three family members with gastric cancer)	PVS1 PM2 PP4	Pathogenic
Chr 16:6886705-68867208 (GRCh37)	NM_004360.3: c.2439 +5_2439 +8delGTAA	NA	Heterozygous	1) Breast NOS 76 2) Endometrial 64	1) None 2) None	2/490,000	NA	van der Post et al. 2015b (patient with DGC, LBC in 50s)	PM2 PP3 PP4	Variant of uncertain significance
Chr 16:68867191 (GRCh37)	NM_004360.3: c.2440-2A>G	NA	Heterozygous	LBC 40s	None	1/490,000	NA	NA	PVS1 PM2 PP3 PP4	Likely pathogenic
Chr 16:68867199 (GRCh37)	NM_004360.3: c.2446A>T	p.Lys816*	Heterozygous	DGC 32	B	1/490,000	NA	NA	PVS1 PM2 PP4	Likely pathogenic
Chr 16:68867227 (GRCh37)	NM_004360.3: c.2474dupC	p.Pro826Alafs*3	Heterozygous	LBC 52	None	1/490,000	NA	NA	PVS1 PM2 PP4	Likely pathogenic
Chr 16:68867243 (GRCh37)	NM_004360.3: c.2490dupG	p.Leu831Alafs*4	Heterozygous	DGC 31	B	1/490,000	NA	NA	PVS1 PM2 PP4	Likely pathogenic
Chr 16:68867259 (GRCh37)	NM_004360.3: c.2506G>T	p.Glu836*	Heterozygous	LBC 54 confirmed de novo	None	1/490,000	NA	NA	PVS1 PS2 PM2 PP4	Likely pathogenic
Chr 16:68867258-68867259 (GRCh37)	NM_004360.3: c.2505_2506dupTG	p.Gln836Valfs*11	Heterozygous	IDC 45	None	1/490,000	NA	NA	PM2	Variant of uncertain significance

(Continued on next page.)

Table 1. (Continued)

Genomic location	HGVs cDNA	HGVs protein	Zygosity	Proband tumor (age)	Family criteria Met (A-F) ^a	Ambry frequency (X/490,000 CDH1 alleles)	Population frequency (gnomAD)	Literature	ACMG/AMP criteria Met ^b	Variant interpretation
Chr 16:68867302-68867303 (GRCh37)	NM_004360.3: c.2549_2550delCC	p.Ser850Phefs*10	Heterozygous	Bilat breast 43 (right: IDC/LBC, left: DCIS)	None	1/490,000	NA	NA	PM2	Variant of uncertain significance
Chr 16:68867347 (GRCh37)	NM_004360.3: c.2594G>A	p.Trp865*	Heterozygous	None	None	1/490,000	NA	NA	PM2	Variant of uncertain significance

Bilat, bilateral; DCIS, ductal carcinoma in situ; DGC, diffuse gastric cancer; GC, gastric cancer; IDC, invasive ductal carcinoma; LBC, lobular breast cancer; LCIS, lobular carcinoma in situ; NOS, not otherwise specified; NP, not provided; NA, not available.

^aCDH1 testing criteria adapted from van der Post et al. (2015a):

A) Two or more GC cases regardless of age, at least one confirmed DGC, in first-degree and second-degree relatives

B) One case of DGC <40

C) Personal or family history of DGC and LBC, one diagnosed <50

D) Bilateral LBC or family history of 2 or more cases of LBC <50

E) A personal or family history of cleft lip/palate in a patient with DGC

F) In situ signet ring cells and/or pagetoid spread of signet ring cells

^bACMG/AMP criteria described by Richards et al. 2015:

PVS1 (pathogenic, very strong evidence): null variant (nonsense, frameshift, canonical ± 1 or 2 splice sites, initiation codon, single, or multiexon deletion) in a gene where LOF is a known mechanism of disease.

PS2 (pathogenic, strong evidence): de novo (both maternity and paternity confirmed) in a patient with the disease and no family history.

PM2 (pathogenic, moderate evidence): absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.

PP3 (pathogenic, supporting evidence): multiple lines of computational evidence support a deleterious effect on the gene or gene product (splicing impact).

PP4 (pathogenic, supporting evidence): patient's phenotype or family history is highly specific for a disease with a single genetic etiology.

Of the two splicing variants identified, c.2439+5_2439+8delGTAA is described in the literature in a family meeting clinical diagnostic criteria for *CDH1* testing (van der Post et al. 2015b). However, its functional effect is uncertain, and, as such, it is classified as a variant of uncertain significance (VUS) at this time. The other splicing variant, c.2440-2A>G, is predicted to affect splicing by in silico tools and was seen in a patient with LBC. It was classified as a likely pathogenic variant because of its position at the canonical splice acceptor site, in silico predictions, and rarity (Table 1).

With regards to the three truncations identified past *CDH1* c.2506G>T (p.Glu836*)—c.2505_2506dupTG (p.Gln836Valfs*11), c.2549_2550delCC (p.Ser850Phefs*10), and c.2594G>A (p.Trp865*)—predicted loss of function was not used in their classification, because of the uncertainty surrounding the clinical relevance of the amino acids located downstream from amino acid position 836. Additionally, none of the reported families met clinical diagnostic criteria for *CDH1* testing. Therefore, the three truncations located downstream from *CDH1* c.2506G>T (p.Glu836*) were classified as VUS (Table 1).

SUMMARY

Carboxy-terminal truncating alterations in *CDH1* may escape the NMD pathway and result in proteins retaining partial function. Because of the uncertainty surrounding the functional impact of these alterations, multiple lines of evidence are essential in determining pathogenicity. Here we describe the most carboxy-terminal *CDH1* clinically actionable alteration in our cohort, in addition to other carboxy-terminal truncations in this gene. Identifying the most distal pathogenic alteration provides evidence to correctly classify other carboxy-terminal truncating variants. This is a critical component to proper patient management that highlights the importance of continued data sharing efforts.

ADDITIONAL INFORMATION

Database Deposition and Access

All interpreted variants are deposited in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) and can be found under accession numbers SCV000700322.1, SCV000218032.4, SCV000187463.4, SCV000700319.1, SCV000700320.1, SCV000665400.1, SCV000580713.2, SCV000661653.1, SCV000665390.1, SCV000185568.4, and SCV000700321.1.

Ethics Statement

This study was approved and carried out in accordance with the recommendations of the Western Institutional Review Board (WIRB), as part of the protocol titled “Sharing the results of genetic functional assessments performed for subjects previously submitted for clinical genomic testing.” Appropriate written informed consent was obtained prior to the collection of study data and the use of this data in analysis and the resulting publication.

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Author Contributions

K.K. and R.K. drove the development of the intellectual concepts, performed analyses, interpreted data, and wrote the manuscript.

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Competing Interest Statement

All authors were employees of Ambry Genetics when they were engaged with this project.

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