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Germline mutations in *CDH1* are infrequent in women with early-onset or familial lobular breast cancers

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ABSTRACT

Background Germline mutations in *CDH1* are associated with hereditary diffuse gastric cancer; lobular breast cancer also occurs excessively in families with such condition.

Method To determine if *CDH1* is a susceptibility gene for lobular breast cancer in women without a family history of diffuse gastric cancer, germline DNA was analysed for the presence of *CDH1* mutations in 318 women with lobular breast cancer who were diagnosed before the age of 45 years or had a family history of breast cancer and were not known, or known not, to be carriers of germline mutations in *BRCA1* or *BRCA2*. Cases were ascertained through breast cancer registries and high-risk cancer genetic clinics (Breast Cancer Family Registry, the kConFab and a consortium of breast cancer genetics clinics in the United States and Spain). Additionally, Multiplex Ligation-dependent Probe Amplification was performed for 134 cases to detect large deletions.

Results No truncating mutations and no large deletions were detected. Six non-synonymous variants were found in seven families. Four (4/318 or 1.3%) are considered to be potentially pathogenic through in vitro and in silico analysis.

Conclusion Potentially pathogenic germline *CDH1* mutations in women with early-onset or familial lobular breast cancer are at most infrequent.

INTRODUCTION

CDH1 encodes the cell–cell adhesion molecule, E-cadherin. Loss of expression of E-cadherin contributes to the infiltrative and metastatic behaviours of cancers. Germline loss-of-function mutations in *CDH1* are associated with the autosomal dominant cancer-predisposition syndrome, hereditary diffuse gastric cancer (HDGC) (OMIM: +192090).[1 2] In HDGC, germline mutations in *CDH1* confer a high lifetime risk of DGC for male and female mutation carriers.[3 4] Additionally, female mutation carriers have a 39%–52% lifetime risk of breast cancer, although these estimates have wide confidence intervals.[3 4] Multiple reports have established the association of lobular breast cancer (LBC) with HDGC and germline mutations in *CDH1*.[4–7]

Previously, we identified one carrier of a germline truncating *CDH1* mutation among 23 women with LBC known not to carry germline *BRCA1* and *BRCA2* mutations.[8] This case series included women diagnosed with LBC at a young age (≦45 years) and women diagnosed with LBC at any age with a family history of breast cancer but not of gastric cancer (1/23 or 4.3%).[8] The same mutation was subsequently confirmed in a relative of the mutation carrier who also had LBC. This coincidence of *CDH1* mutations and hereditary LBC led us to assess the prevalence of *CDH1* mutations in a series of 318 women with early-onset LBC or a family history of breast cancer, consistent with hereditary LBC, ascertained through breast cancer registries and high-risk cancer genetic clinics (Breast Cancer Family Registry (Breast CFR), the kConFab and a consortium of breast cancer genetics clinics in the United States and Spain).

MATERIALS AND METHODS

Patient accrual, preparation of DNA and *CDH1* sequencing, deletion analysis, mutation validation, and protein structure and functional analyses are described in the online supplementary material.

RESULTS

Germline DNAs from 327 eligible patients with LBC were analysed for variants in *CDH1*, but for nine samples, several exons failed to amplify, yielding incomplete results. Sequence analysis for heterozygous variants in the 318 patients with complete results did not detect any protein-truncating mutations. Multiplex Ligation-dependent Probe Amplification analyses in 134 patients did not reveal any large deletions in *CDH1*.

We did find 10 patients with non-synonymous variants. One non-synonymous change, c.1774G→A, p.A592T, was found in two patients and is a known germline variant that is not associated with risk of familial breast cancer or HDGC.[9 10] The variant, c.2494G→A, p.V832M, which had previously been identified in a patient with HDGC and was functionally characterised as a pathogenic mutation,[11 12] was found in a woman who was diagnosed as having LBC at the age of 43 years and had a family history of ductal breast cancer in a sister and unspecified breast cancer in a maternal aunt. Segregation analysis has not yet been performed. The remaining non-synonymous variants were novel and did not appear in any

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public databases. These variants were c.8C→G, p.P3R; c.1223C→T, p.A408V; c.1297G→A, p.D433N; c.1813A→G, p.R695G and c.88 C→A, p.P30T, which were found in two patients not known to be related. There was no family history of gastric cancer for any of the patients who carried novel non-synonymous variants (table 1).

Nine unreported novel silent changes were identified: five synonymous variants in exons and four variants in introns. Two of these novel changes were found in more than one patient (data not shown).

We performed several tests to assess the likelihood that any of the non-synonymous variants resulted in a loss of normal function. Web-based software (Sorting Intolerant from Tolerant, SIFT) that predicts whether the amino acid change conferred by non-synonymous variants might alter protein structure, and thus possibly function, indicated that all but one variant, c.8C→G, p.P3R, which occurred in the signal peptide of the pre-protein, should be tolerated and therefore is unlikely to be pathogenic. Moreover, web-based software (Berkeley Drosophila Genome Project, Splice Site Prediction by Neural Network, Berkeley, Calif) did not predict alteration of splicing by any of the novel synonymous or non-synonymous variants or intronic variants identified.

The likely pathogenicities of the novel non-synonymous variants were further assessed by analysing the predicted effects of amino acid changes on the three-dimensional structure of E-cadherin. Because the coordinates of the three-dimensional structure of the ectodomain of E-cadherin were not available, we used the model of the closely related paralog, C-cadherin, to predict likely changes in the structure. One of the mutations, c.1223C→T, p.A408V, changes the alanine residue, which is well-conserved in this family of proteins, to bulkier valine and is located in calcium ion-binding extracellular domain 3. Surface modelling of the mutated protein indicated that this bulky valine could conceivably alter the binding pocket of one of three calcium ions that mediate homotypic cadherin domain interactions (Supplementary figure 1). Another mutation, c.1297G→A, p.D433N, was also found to be located in close proximity to this calcium-binding site (Supplementary figure 1). Because the c.8C→G, p.P3R variant occurs in the signal peptide of the precursor protein and had been predicted to be pathogenic, we hypothesised that this variant could result in mislocalisation or lack of expression of E-cadherin on the cell surface. To test this hypothesis, we expressed normal E-cadherin or each of the mutated versions of the protein in cells lacking endogenous E-cadherin. As seen in Supplementary figure 2, E-cadherin mutated with the c.8C→G, p.P3R variant did exhibit membrane localisation, indicating that protein localisation was not grossly affected by this variant. Additionally, the other novel non-synonymous variants also demonstrated membrane localisation (data not shown). However, because the levels at which we expressed E-cadherin were not physiological, it is possible that subtle effects of the mutations could have been missed.

Taking into account the in vitro and in silico analysis, four non-synonymous variants (c.8C→G, p.P3R; c.1223C→T, p.A408V; c.1297G→A, p.D433N and c.2494G→A, p.V832M) are considered potentially pathogenic (4/318 or 1.3%). If we only consider the subset of patients who have been tested and found not to carry *BRCA1* or *BRCA2* mutations, the prevalence of potentially pathogenic variants is 1.6% (4/246).

DISCUSSION

Germline mutations in *CDH1* are associated with a substantively increased risk of LBC.[8] This study found that the prevalence of potentially pathogenic *CDH1* variants is low in patients with early-onset or familial LBC who do not report a clear

Table 1 Clinical characteristics of patients with LBC with non-synonymous variants

Non-synonymous variant	Criteria 1 or 2	*BRCA1/2* mutation status	Age at diagnosis	Family history (age at diagnosis)
c.8C→G, p.P3R	1	Negative	38 years	Maternal aunt=breast cancer (46 years) Maternal aunt=breast cancer (67 years) Maternal cousin=breast cancer (42 years) Mother=retroperitoneal tumour Paternal grandmother=breast cancer
c.88 C→A, p.P30T (two patients)	1	Unknown	40 years	
	2	Negative	47 years	Paternal aunt=breast cancer (40 years) Female paternal cousin=breast cancer (40 years) Male paternal cousin=breast cancer (50 years) Female paternal cousin=breast cancer (47 years)
c.1223C→T, p.A408V	1	Negative	44 years	No cancers
c.1297G→A, p.D433N	1	Negative	41 years	Paternal grandmother=intestinal cancer Maternal grandmother=lung cancer Maternal grandfather=mouth cancer
c.1813A→G, p.R605G	1	Unknown	42 years	Mother=breast cancer (60 years) Maternal uncle=pancreatic cancer (64 years)
c. 2494G→A, p.V832M (known missense mutation in HDGC)	1	Negative	43 years	Sister=ductal breast cancer Maternal aunt=breast cancer Paternal uncle=leukaemia Paternal grandmother=colon cancer

Clinical history of patients with LBC in whom potentially pathogenic variants were identified. There was no known family history of gastric cancer in these patients.

family history of DGC. The large sample size increases the likelihood that the results in this setting are precise. This study highlights the utility of publicly available registries as valuable resources of clinically and epidemiologically annotated families with accompanying germline DNA for future research in this field.

It remains possible that *CDH1* mutations are present in rare families with multiple LBCs even without gastric cancer. Although the patients in the present study had confirmed LBC, we were unable to confirm the pathology of the breast cancers in the relatives, which remained unspecified for most of the patients. Additionally, because 72 patients (23%) were not tested for mutations in *BRCA1* and *BRCA2* (table 2), it is possible that some *BRCA1* and *BRCA2* mutation carriers were included in this study. The likelihood, however, is low because most early-onset and familial breast cancers are not accounted for by germline mutations in *BRCA1* and *BRCA2*.[13 14] We had previously reported a pathogenic truncating *CDH1* mutation in a patient with LBC and her mother, who had both developed LBC before age 45 years.[8] However, our data suggest that *CDH1*-associated LBC without gastric cancer must be very rare because so few were identified in the present study among women highly selected for early-onset LBC or LBC with additional breast cancer in the family. It might still be prudent to consider germline *CDH1* testing in families with confirmed multiple cases of early-onset LBC, even in the absence of a family history of gastric cancer. In such families, and in those with a reported but unspecified history of abdominal cancer, the possibility of ovarian cancer would lead to *BRCA1* and then *BRCA2* testing, and the possibility of DGC should lead to consideration of *CDH1* testing. For women with LBC, it is important to look for a family history of gastric cancer so that HDGC families will be recognised and offered appropriate management for their risk of DGC.

In our study, the pathogenic germline variant, p.V832M, was identified in a patient with LBC without a family history of gastric cancer. This variant was initially found to segregate with disease in a Japanese family where the proband had DGC at age 61 years and four of seven siblings, the mother and a niece all had unspecified gastric cancer. Functional characterisation in Chinese hamster ovary cells demonstrated reduced cell aggregation and increased invasive properties of the mutant compared with wild-type E-cadherin.[12] Although this effect was not reproduced in functional characterisation undertaken in human squamous epithelial cells,[15] further work has demonstrated a mechanism by which this mutation might confer a pathogenic effect, through loss of type Iγ phosphatidylinositol phosphate kinase binding, causing abnormal E-cadherin trafficking and adherens junction formation.[16]

The novel non-synonymous variants in this study were not confirmed by our in vitro and in silico studies to be pathogenic, although further investigation needs to be done on the suggestive evidence that the variants c.1223C→T, p.A408V and c.1297G→A, p.D433N might interfere with calcium-dependent homophilic binding. Also, a novel, presumably rare variant (c.88 C→A, p.P30T) was shared by two patients with LBC from one of the high-risk breast cancer clinics: this could imply that this variant is linked to the disease and that these two women are distantly related. Alternatively, this may represent a rare variant not associated with LBC, whose distribution in the normal population frequency will become known as the genomes of more people are sequenced. Data from the 1000 Genomes Project may also be helpful in the interpretation of the significance of these variants, through demonstration of the full profile of

Table 2 Criteria for ascertainment for *CDH1* mutation analysis

Breast Cancer Genetics Consortium							
Criteria for ascertainment	Patients (n=120)	Sex	Median age (years)	Age range (years)	Novel non-synonymous variants in criteria	*BRCA1/2* negative (n=66)	*BRCA1/2* unknown (n=54)
Criteria 1	66	F	40	(28–44) (n=66)	2	36	34
Criteria 2	54	F	54	(45–72) (n=54)	1	30	20
Breast CFR							
Criteria for ascertainment	Patients (n=165)	Sex	Median age (years)	Age range (years)	Novel non-synonymous variants in criteria	*BRCA1/2* negative (n=147)	*BRCA1/2* unknown (n=18)
Criteria 1	142	F	40	(31–44) (n=51)	3	130	12
Criteria 2	23	F	57	(45–79) (n=20)	0	17	6
kConFab							
Criteria for ascertainment	Patients (n=33)	Sex	Median age (years)	Age range (years)	Novel non-synonymous variants in criteria	*BRCA1/2* negative (n=33)	*BRCA1/2* unknown
Criteria 1	6	F	40	(37–43) (n=6)	0	6	0
Criteria 2	27	F	57	(45–77) (n=28)	0	27	0
All samples							
Criteria for ascertainment	Patients (n=318)	Sex	Median age (years)	Age range (years)	Novel non-synonymous variants in criteria	*BRCA1/2* negative (n=246)	*BRCA1/2* unknown (n=72)
Criteria 1	214	F	40	(28–44) (n=123)	5	172	46
Criteria 2	104	F	56	(45–79) (n=101)	1	74	26

The criteria for ascertainment were a patient with a history of lobular or mixed ductal and lobular pathology whose *BRCA1* and *BRCA2* mutation status was negative or unknown and either diagnosed before age 45 years or diagnosed at any age but with two or more cases of breast cancer in first- or second-degree relatives.

normal variation within *CDH1* and their distribution in and across populations.

Although a combination of LBC and DGC is strongly indicative of germline mutations in *CDH1*, in the absence of a history of DGC, *CDH1* mutations appear to be extremely rare. It is possible that *CDH1* mutations would be more often identified in families with multiple documented invasive lobular or mixed ductal/lobular breast cancers in the absence of DGC, but such families are uncommon. Therefore, a history of early-onset or familial LBC should trigger specific questions around a history of abdominal cancer.

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