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Germline *CDH1* mutations in bilateral lobular carcinoma *in situ*

C Petridis*[,1,2], I Shinomiya[1], K Kohut[3], P Gorman[3], M Caneppele[3], V Shah[1], M Troy[1], S E Pinder[1], A Hanby[4], I Tomlinson[5], R C Trembath[2], R Roylance[3], M A Simpson[2] and E J Sawyer[1]

[1]*Research Oncology, Kings College London, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK;* [2]*Medical and Molecular Genetics, Kings College London, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK;* [3]*Centre for Molecular Oncology, Barts Cancer Institute, Queen Mary, University of London, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, UK;* [4]*Leeds Institute of Molecular Medicine, Wellcome Trust Brenner Building, St James's University Hospital, Leeds LS9 7TF, UK and* [5]*The Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK*

Background: Invasive lobular breast cancer (ILC) and lobular carcinoma *in situ* (LCIS) are characterised by loss of E-cadherin expression. However germline *CDH1* mutations are rare in cases of ILC with no family history of hereditary diffuse gastric cancer (HDGC) and have not been described in women with LCIS.

Methods: We screened the *CDH1* gene in 50 cases of bilateral LCIS/ILC using Sanger sequencing and MLPA.

Results: Sanger sequencing revealed four pathogenic germline mutations, including a novel splicing mutation (c.48+1G>A). The remaining three (c.1465insC, c.1942G>T, c.2398delC) have been previously described. All four cases had bilateral LCIS +/− ILC and no family history of gastric cancer.

Conclusion: *CDH1* germline mutations have not been previously described in women with LCIS. We have shown that germline *CDH1* mutations are associated with early onset of bilateral LCIS with or without ILC in women without a family history of gastric cancer. *CDH1* mutation screening should be considered in women with early onset of bilateral LCIS/ILC with no family history of HDGC.

Invasive lobular breast cancer (ILC) accounts for 10–15% of invasive breast cancers and has distinct clinical and molecular characteristics compared with the more common invasive carcinoma of ductal/no special type (IDC). ILC is often associated with lobular carcinoma *in situ* (LCIS), a clinically undetectable form of non-invasive breast cancer. LCIS is typically found incidentally on biopsy and is being more commonly detected with the advent of screening mammography. ILC and LCIS are characterised by loss of expression of E-cadherin, which is due to a combination of somatic mutations, loss of heterozygosity and hypermethylation (Droufakou *et al*, 2001). Although LCIS shares many of the same genetic aberrations as ILC, suggesting that it is a precursor lesion, it is also a risk factor for developing invasive cancer in the contralateral breast (Fisher *et al*, 2004). Women who have had LCIS are 2.4 times more likely to develop invasive breast cancer compared with the general population (Chuba *et al*, 2005). These invasive cancers are not solely ILC, although there is an excess of ILC (23–88% of cases) (Fisher *et al*, 2004, Chuba *et al*, 2005). This together with the increased risk of contralateral breast cancer has led to debate as to whether LCIS should be regarded as a risk factor for breast cancer rather than a true precursor lesion.

Claus *et al* showed that LCIS was more likely to be bilateral rather than other histologic subtypes: 27% of LCIS cases in their series were bilateral compared with 5% of DCIS, 7% of ILC and 2% of IDC. In addition, cases of LCIS were significantly more likely to have a first-degree relative affected with breast cancer (23% of LCIS, 12% of DCIS, 11% of ILC and 12% of IDC). These findings suggest that LCIS is likely to have a genetic component, however only a minority of the LCIS cases in this series were both bilateral and reported a family history of breast cancer (Claus *et al*, 1993).

*Correspondence: C Petridis; E-mail: christos.petridis@kcl.ac.uk

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Germline *CDH1* mutations were initially reported in patients with hereditary diffuse gastric cancer (HDGC) (Guilford *et al*, 1998). Approximately 30% of families with HDGC due to *CDH1* germline mutations also include individuals with ILC (Pharoah *et al*, 2001; Brooks–Wilson *et al*, 2004; Suriano *et al*, 2005; Kaurah *et al*, 2007). However, germline *CDH1* mutations in women with ILC that are present without a family history of HDGC appear to be rare. Of the 408 cases of LCIS/ILC with no family history of HDGC screened for *CDH1* mutations and reported in the literature, only three germline mutations have been described, all in cases of ILC (Rahman *et al*, 2000; Masciari *et al*, 2007; Schrader *et al*, 2011; Xie *et al*, 2011) (Table 1). The cases in these studies were selected mainly on the basis of early onset disease or family history of ILC.

In the current study, we aimed to assess the frequency of germline mutations in *CDH1* in bilateral LCIS or ILC testing the hypothesis that cases of bilateral LCIS/ILC are more likely to have an inherited component to their disease. This hypothesis is supported by a recent retrospective study from France of all 165 index cases who had undergone *CDH1* mutation screening in their region from 2006 to 2012. They identified 18 individuals with *CDH1* mutations, three of which had bilateral ILC before the age of 50 prior to developing gastric cancer (Benusiglio *et al*, 2013).

MATERIALS AND METHODS

The GLACIER (Genetics of lobular carcinoma *in situ* in Europe) study, MREC 06/Q1702/64, has ascertained patients from throughout the UK with the aim of understanding genetic predisposition to LCIS and/or ILC. Any women aged 60 or less at the time of diagnosis, with a current or past history of LCIS (with or without invasive disease of any morphological subtype) or pure ILC were eligible. At the time of this analysis, 2210 cases of LCIS/ILC had been recruited from 97 UK hospitals and diagnosis was confirmed from local pathology reports in 1960 cases. Peripheral blood samples and formalin fixed paraffin embedded (FFPE) tissue blocks were collected from participants along with family history data and other risk factor information.

We identified 50 cases of bilateral LCIS/ILC from the GLACIER study of European ethnicity. Cases were considered bilateral if they had evidence of bilateral LCIS with or without invasive carcinoma, or pure ILC either synchronously or sequentially. All cases with FFPE tissue blocks ($n=25$) underwent histological review to confirm the diagnosis (SEP, AH). None had the histological diagnosis changed following the review.

Germline DNA was extracted from peripheral blood samples using the Nucleon product chemistry (Tepnel, Manchester, UK) and quantified using PicoGreen. The entire coding sequence and associated splice sites of the *CDH1* gene were screened by Sanger sequencing using standard techniques. Exon flanking intronic primers were designed using Primer3 (http://frodo.wi.mit.edu/), DNA fragments amplified by PCR and PCR products were sequenced on the ABI 3730 Genetic Analyser (Applied Biosystems, San Francisco, CA, USA) using BDT V3.1. MLPA (Multiplex Ligation-dependent Probe Amplification) was performed to detect any large-scale deletions using the MRC Holland kit. DNA samples were amplified and PCR products were analysed on the ABI 3730 Genetic Analyser (Applied Biosystems) using TAMRA 500, as per the manufacturers instructions. Coffalyser (MRC Holland, Amsterdam, The Netherland) was used to call potential exonic deletions/rearrangements.

For statistical analysis, Fisher's exact test has been used for binary data and the Mann–Whitney U-test for continuous data (R v2.15.1).

Table 1. Published breast cancer studies that screened the *CDH1* gene for germline mutations in cases with no family history of gastric cancer

Studies	Phenotypes	Mutation carriers	Total cases
Current study	Bilateral LCIS/ILC	4	50
	FH of breast cancer[a]	2	27
	Early onset (<45 years)	2	7
	Bilateral LCIS/ILC	4	50
Rahman *et al*, 2000	LCIS	0	65
	FH of breast cancer	0	20
	Early onset (<45 years)	0	Unknown
	Bilateral LCIS	0	17
Masciari *et al*, 2007	9 ILC/14 mixed pathology	1	23
	FH of breast cancer	1	19
	Early onset (<45 years)	1	4
	Bilateral ILC	Unknown	Unknown
Schrader *et al*, 2011	ILC	0	318
	FH of breast cancer	0	104
	Early onset (<45 years)	0	214
	Bilateral ILC	0	Unknown
Xie *et al*, 2011	Familial ILC[b]	2	2
	FH of breast cancer	2	2
	Early onset (<45 years)	1	1
	Bilateral ILC	2	2

Abbreviations: ILC = invasive lobular breast cancer; LCIS = lobular carcinoma *in situ*.
[a]Not confined to first-degree relative.
[b]Index case only described, Family A, 5 ILC cases, 2 bilateral; Family B, 1 ILC.

RESULTS

The characteristics of each bilateral case are summarised in Supplementary Table 1. The majority of patients had bilateral LCIS with or without invasive disease. One case had bilateral ILC with no LCIS and four had bilateral ILC with unilateral LCIS. The median age for pure bilateral LCIS was 49 years (range 44–56, IQR = 5.5) and for LCIS with ILC was 51 years (range 36–60, IQR = 6), Supplementary Table 2. The median age of diagnosis for all the 50 bilateral cases was 51 years (range 36–60, IQR = 6), which was similar to the median age for the 1791 unilateral cases (51 years) of LCIS/ILC (all non-European cases excluded) collected through GLACIER ($P=0.89$, Mann–Whitney U-test). Family history of breast cancer (not confined to first-degree relative) was more frequent in bilateral cases (56%) than unilateral (41%) ($P=0.042$, Fisher's exact test). There was no excess of a family history of gastric cancer in patients with bilateral disease (10%) compared with unilateral (8%) ($P=0.61$ Fisher's exact test, Supplementary Table 3).

Four germline mutations were identified in four individuals: one donor splice-site mutation (c.48 + 1G > A), two frame-shift mutations (c.1465insC, c.2398delC) and a nonsense substitution (c.1942G > T), (Table 2, Figure 1). The c.48 + 1G > A mutation is novel, affecting the donor splice site of intron 1 and occurred in an individual with bilateral LCIS and ILC at the age of 51 with a family history of breast cancer. The other three mutations introduce a premature stop codon in exon 10, 13 and 15 respectively, leading to a protein lacking all or a part of the intracellular domain. These three mutations have been previously

Table 2. Pathogenic mutations found in four cases

Sample ID	Exon	Nucleotide substitution	Amino-acid substitution	Age of diagnosis	Pathology
BILAT-044	1	c.48 + 1G > A	Donor splice site	51	Bilateral LCIS, Bilateral ILC
BILAT-005	10	c.1465insC	p.P489fs	46	Bilateral LCIS, No ILC
BILAT-039	13	c.1942G > T	p.E648X	40	Bilateral LCIS, Unilateral ILC
BILAT-021	15	c.2398delC	p.P799fs	37	Bilateral LCIS, Unilateral ILC

Abbreviations: ILC = invasive lobular breast cancer; LCIS = lobular carcinoma *in situ*.

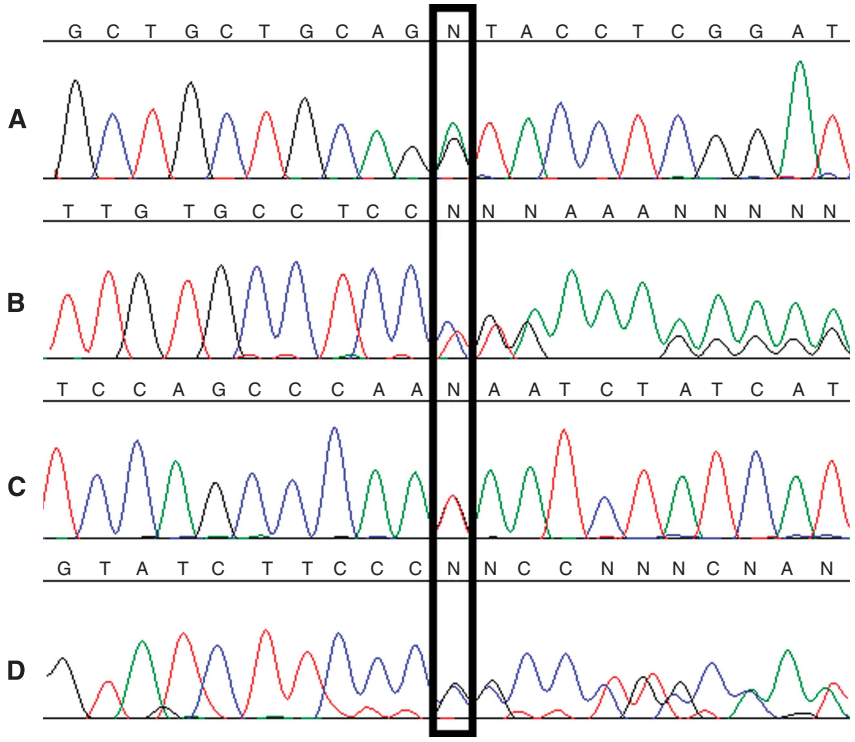

Figure 1. Chromatograms of four germline mutations (A) c.48 + 1G > A, (B) c.1465insC, (C) c.1942G > T and (D) c.2398delC.

described as follows: c.1942G > T, a somatic mutation in colon cancer (Cancer Genome Atlas Network, 2012); c.1465insC, a germline mutation in diffuse gastric cancer (Barber *et al*, 2008); and c.2398delC, a founder mutation in four Newfoundland families with diffuse gastric and ILC (Kaurah *et al*, 2007). The c.1465insC mutation occurred in an individual with bilateral pure LCIS at the age of 46 whose mother had breast cancer at the age of 43. The remaining two carriers had bilateral LCIS and unilateral concurrent ILC with no family history of breast cancer. None of the four cases had a family history of gastric cancer. There was no evidence of exonic deletions in any of the remaining 46 cases without a germline mutation using MPLA.

Using a control dataset (no personal history of breast cancer) from the King's College London exome sequencing database, we have found no truncating or splice-site mutations in *CDH1* of 190 ethnicity matched individuals with no personal history of breast cancer ($P = 0.002$, Fisher's exact test).

DISCUSSION

Four (8%) of the bilateral cases in our cohort of LCIS/ILC were found to have a germline mutation in *CDH1*. All are predicted to be loss of function, with one being a splicing mutation and the remaining three being truncating mutations. Two have previously been shown to be pathogenic. The frequency of *CDH1* mutations is much higher than previous studies of LCIS/ILC without a personal or family history of gastric cancer where only 0.7% of the sporadic or familial cases of LCIS/ILC without HDGC carry *CDH1* mutations ($P = 0.003$, Fisher's exact test), (Table 1). The median age of the mutation carriers at presentation was eight years lower than that for the other 46 bilateral cases (43 years *vs* 51 years). Interestingly only two cases had a family history of breast cancer with one having a first-degree relative with the disease (subtype unknown) and none had any family history of gastric cancer.

One of the limitations of our study is that family history is self-reported by the index case and we are therefore unable to ascertain what subtype of breast or gastric cancer the family members suffered from. It does not appear that there is an excess of personal or family history of gastric cancer in the GLACIER cohort when comparing it with the UK statistics produced by the Cancer Research UK, but we cannot be certain that diffuse gastric cancer is not overrepresented in our bilateral cases.

We have shown for the first time that *CDH1* mutations predispose to LCIS, with 12.5% (1 out of 8) of bilateral pure LCIS and 11.5% (3 out of 26) of bilateral LCIS with ILC having *CDH1*

Table 3. Current *CDH1* testing criteria and potential new criteria

***CDH1* testing criteria**	**Definition**	**Cases that meet criteria in this study**	**Number of cases with *CDH1* mutation in this study**
Current (Fitzgerald *et al*)	2 GC cases in family, one confirmed DGC age <50	0	0
	3 confirmed DGC cases in 1st or 2nd degree relatives any age	0	0
	DGC age <40	0	0
	Personal or family history of DGC and ILC, 1 dx <50	1	0
New criterion suggested by Benusiglio *et al*	Personal or family history of 2 ILC age <50[a]	3	0
New criterion suggested current study with different age thresholds	Bilateral LCIS/ILC age <55	41	4 (10%)
	Bilateral LCIS/ILC age <50	21	3 (14%)
	Bilateral LCIS/ILC age <45	7	2 (29%)

Abbreviations: DGC = diffuse gastric cancer; ILC = invasive lobular breast cancer; LCIS = lobular carcinoma *in situ*.
[a]After exclusion of BRCA1/2 mutation.

mutations in this study. Interestingly, none of the cases with bilateral LCIS and non-lobular invasive disease (11 cases) had *CDH1* mutations, suggesting that the presence of a germline *CDH1* mutation in bilateral LCIS predisposes to the development of ILC rather than IDC. In the study by Rahman *et al*, only 17 cases (26%) of the 65 cases of LCIS screened had bilateral disease, (Table 1), which may explain why no *CDH1* mutations were detected.

None of our four mutation carriers satisfy the current criteria for *CDH1* testing given the necessity to have a family HDGC in order to be eligible for screening (Table 3). Although they gave no family history of gastric cancer it is possible that they may develop diffuse gastric cancer (DGC) in the future, as Pharoah *et al*, 2001 showed that the estimated cumulative risk of gastric cancer is higher (83%) than that for breast cancer (39%) in women with *CDH1* mutations. However, this was calculated using families with at least three cases of DGC and, as discussed by Pharoah *et al*, may not apply to individuals with a minimal family history, in whom the risks are likely to be lower (Pharoah *et al,* 2001).

Benusiglio *et al* suggested that women with a personal or family history of at least two ILC before the age of 50 should be offered *CDH1* screening. However, none of the four carrier cases identified in our study would fulfil these criteria as they do not take into account bilateral LCIS. On the basis of our study, we recommend that this should be extended to include women with bilateral LCIS. Using an age threshold of less than 50 years would miss some *CDH1* mutation carriers. Lowering the age threshold further to less than 45 years for mutation screening would result in 28% of eligible patients having a *CDH1* mutation in this study, Table 3.

The current consensus guidelines recommend annual mammography and breast MRI starting at the age of 35 for *CDH1* mutation carriers (Fitzgerald *et al*, 2010). This differs from the current UK screening recommendations for the *BRCA1/2* carriers who are offered annual MRI surveillance, aged 30–49 years, and then annual mammography from the age of 50 and only continue MRI surveillance if there is evidence of a dense breast pattern (guidance.nice.org.uk/cg164). As MRI has been shown to have the lowest false negative rate in detecting ILC compared with mammography and ultrasound, and is routinely used for pre-operative work-up of ILC, it would seem prudent to continue MRI surveillance in *CDH1* carriers rather than switch to mammography alone at the age of 50 (Boetes *et al,* 2004). In addition, two studies have shown a small benefit for MRI screening in LCIS over mammography (Port *et al,* 2007; Sung *et al,* 2011). *CDH1* carriers may also benefit from chemoprevention as the NSABP Breast Cancer Prevention Trial (P-1) study showed that women with a history of LCIS who took tamoxifen had almost half the risk (relative risk = 0.54) of developing an invasive cancer rather than women with a history of LCIS randomised to placebo (Fisher *et al,* 2005). As the penetrance of gastric cancer in *CDH1* carriers with bilateral LCIS/ILC and no family history of DGC is not known, it is difficult to recommend prophylactic gastrectomy in these cases. Annual endoscopic surveillance would be a reasonable alternative until further data is available.

In conclusion, two studies including our own, have shown that *CDH1* mutations in bilateral LCIS or ILC are more common than previously thought (Benusiglio *et al,* 2013). If further studies confirm these findings then, *CDH1* testing could be offered to individuals with bilateral LCIS/ILC under the age of 50, enabling us to identify patients with *CDH1* mutations who may benefit from regular breast MRI screening and endoscopic surveillance for diffuse gastric cancer.

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