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Hereditary diffuse gastric cancer: association with lobular breast cancer

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Abstract Hereditary diffuse gastric cancer (HDGC) has been shown to be caused by germline mutations in the gene *CDH1* located at 16q22.1, which encodes the cell–cell adhesion molecule, E-cadherin. Not only does loss of expression of E-cadherin account for the morphologic differences between intestinal and diffuse gastric cancer (DGC) variants, but it also appears to lead to distinct cellular features which appear to be common amongst related cancers that have been seen in the syndrome. As in most hereditary cancer syndromes, multiple organ sites may be commonly affected by cancer, in HDGC, lobular carcinoma of the breast (LBC) and possibly other organ sites have been shown to be associated with the familial cancer syndrome. Given the complexity of HDGC, not only with regard to the management of the DGC risk, but also with regard to the risk for other related cancers, such as LBC, a multi-disciplinary approach is needed for the management of individuals with known *CDH1* mutations.

Keywords Hereditary diffuse gastric cancer (HDGC) · Diffuse gastric cancer · E-cadherin mutation · *CDH1* mutation · Lobular breast cancer · Screening · Prophylactic total gastrectomy

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Abbreviations

DGC	diffuse gastric cancer
GC	gastric cancer
HDGC	hereditary diffuse gastric cancer
LBC	lobular breast cancer

Introduction

Despite an overall decrease in the global incidence of gastric cancer (GC) [1], the incidence of the subtype, diffuse gastric cancer (DGC) has remained stable and may even be increasing [2]. Within the past ten years, germline mutations in *CDH1*, which encodes E-cadherin, have been found [3] in over 50% of hereditary diffuse gastric cancer (HDGC) families with at least two cases of GC, with one diagnosed as DGC before the age of 50 years [4]. Within these HDGC families, we and others have noted an over-representation of lobular breast cancer (LBC) [4–8]. This observation has led to efforts to determine whether or not *CDH1* is a breast cancer susceptibility gene, distinct from

its gastric cancer risk. Recently our group has reported a novel germline *CDH1* truncating mutation (517insA) in an LBC family with no known history of GC [9]. Within this review we report a germline *CDH1* mutation in a second family in which breast cancer is the predominant cancer diagnosis. The management of HDGC in all patients with a particular focus on the management of the breast cancer risk associated with germline *CDH1* mutations will be discussed.

Methods

The described family was referred to the ongoing HDGC study at the British Columbia Cancer Agency from a cancer genetics clinic in Seattle, WA, USA. Informed consent was obtained from the proband by the referring genetic counselor following ascertainment of a detailed cancer family history and appropriate genetic counseling prior to germline mutation testing. Our laboratory carried out the molecular genetic testing for the *CDH1* mutation on a research basis. Approval for the HDGC study is by the clinical research ethics board of the University of British Columbia.

The proband (IV-4) was diagnosed with widely metastatic lobular breast cancer at age 53 years (Fig. 1a). Her family, of European ancestry, had a history of breast cancer diagnoses occurring in an autosomal dominant fashion on the maternal side of the family where her mother, aunt, and first cousin developed breast cancer in their 50's. Due to her high-risk pedigree *BRCA1*, *BRCA2*, and *PTEN* genetic testing was undertaken and all were negative. *CDH1* testing was also pursued.

Results

All 16 exons were amplified for DHPLC analysis [6]. For exon 10 of *CDH1*, the initial amplicon failed and was therefore analyzed by direct sequencing and thus revealed a donor splice site mutation, 1565 + 1G > A (Fig. 1b). Due to its position at a donor splice site, this mutation is regarded as pathogenic [10].

The proband's sisters (IV-2 and IV-6) participated in all aspects of the proband's genetic consultation. They were appropriately concerned about their risk of breast cancer, but had not thought much about the possibility of getting gastric cancer until the *CDH1* mutation was found. IV-2 and IV-6 had predictive genetic testing for the *CDH1* mutation testing and both were found to be negative. Other family members are being informed about the availability of predictive genetic testing.

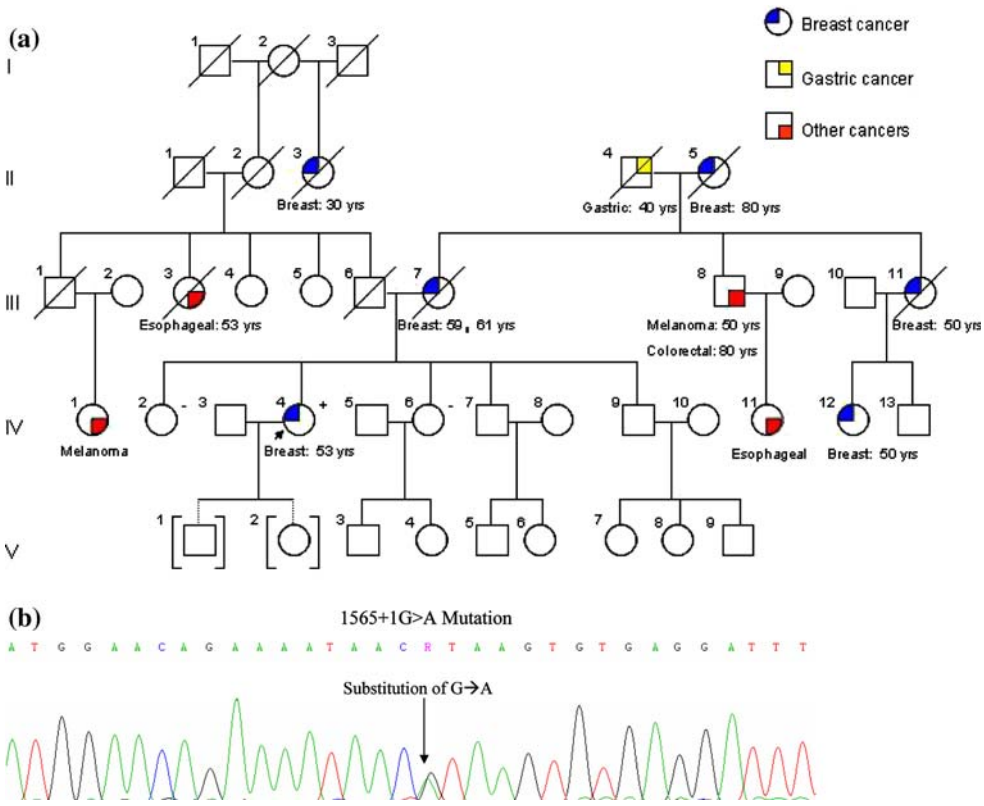

Fig. 1 (**a**) Pedigree of family reported showing a predominance of breast cancer. (**b**) Sequence from family carrying 1565 + 1G→A mutation

Discussion

E-cadherin

CDH1 (OMIM *192090), located on chromosome 16q22.1 encodes, E-cadherin, an epithelial transmembrane cell–cell adhesion molecule and member of the cadherin superfamily of glycoproteins. In a zipper-like fashion, its extracellular domain forms calcium-dependent homodimers between the E-cadherin molecules of adjacent epithelial cells, to act as the primary mediator of epithelial cell adhesion at the adherens junction complex [11]. Through interactions of its cytoplasmic tail with multiple signalling and structural molecules, such as the catenins, E-cadherin, maintains cellular adhesion and epithelial architecture with this link to the cytoskeleton. The cytoplasmic tail of E-cadherin directly associates with β-catenin and γ-catenin which in turn binds to the f-actin microfilaments of the cytoskeleton, directly or through α-catenin [12]. p120-catenin also associates with E-cadherin's cytoplasmic tail at a different site, the juxtamembrane domain, and acts to both strengthen the adhesion between cells and regulate cadherin membrane trafficking and degradation [13, 14]. E-cadherin is considered to have an invasion suppressor role, where decreased expression permits cells to dissociate from each other in order to migrate and invade [15]. In cancers, this manifests as increased infiltrative and metastatic potential [16]. E-cadherin is also thought to act as a tumour suppressor, potentially through its interaction with the multipurpose β -catenin molecule which is an effector of the WNT signalling pathway [17]. Loss of E-cadherin can result in β-catenin release from the membrane and translocation to the nucleus where it complexes with Tcf/Lef-1 transcription factors to initiate transcription of WNT responsive genes [18]. Activation of these genes have been implicated in tumourigenesis through the WNT signalling pathway as seen in adenomatous polyposis coli (APC) [19]. In support of the role of E-cadherin as a tumour suppressor is the observation of abnormal or absent E-cadherin expression in precursor lesions of DGC and LBC, where the phenomenon is seen in in situ signet ring cell carcinomas found in prophylactic gastrectomy specimens from germline *CDH1* mutation carriers [20] and the lobular carcinoma in situ lesions seen adjacent to invasive lobular breast cancers [21]. These examples suggest that loss of E-cadherin is an early or even tumour-initiating event, however the actual molecular basis of such a potential role of E-cadherin in such cases is unknown.

Inactivating *CDH1* mutations are found in 50% of sporadic DGCs [22, 23] and cluster between exons seven and nine [11], in contrast with the low percentage of mutations seen in sporadic intestinal type GCs [23]. Decreased expression of E-cadherin in DGCs may account for morphologic differences between intestinal and DGC variants [24]. Unlike somatic *CDH1* mutations, germline mutations associated with DGC are distributed throughout the gene [7] (Fig. 2). In the cancers from individuals with *CDH1* mutations, *CDH1* acts as a classic tumour suppressor gene with loss of expression of the wildtype allele [25, 26]. In a single study of 6 hereditary DGC cancers, inactivation of the wild-type allele could be attributed to promoter hypermethylation in 5 (83%) of cases [26]. This finding warrants verification in a larger cohort as abnormal promoter methylation in early cancers could potentially form the basis of a screening test.

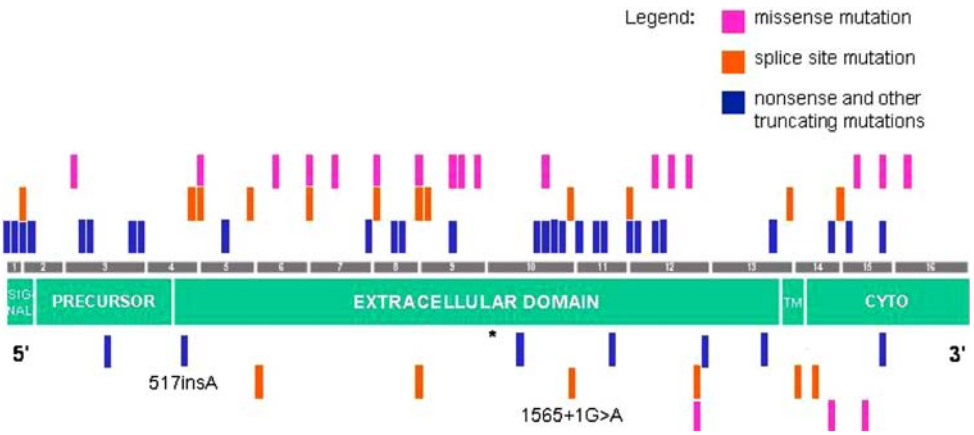

Fig. 2 DGC and LBC associated *CDH1* germline mutations. Mutations shown above *CDH1* gene schematic occur in families with DGC history and those below *CDH1* occur in families with an additional or exclusive LBC history. In addition to the known *CDH1* germline mutations compiled by Kaurah et al. [4], the recent mutation in an LBC family [9] and novel mutation from this paper are shown and identified below the symbol denoting mutation type. * Denotes the halfway point of the *CDH1* coding sequence (1324 or the start of exon 10)

Lobular breast cancer and diffuse gastric cancer: loss of E-cadherin

Currently germline mutations in single genes account for approximately 5–10% of breast cancer [27]. High penetrance genes such as *BRCA1* and *2* account for 3–8%, and *TP53* and *PTEN* as seen in Li-Fraumeni and Cowden syndrome together only account for <0.1% of breast cancer diagnoses [28]. Other medium and low penetrance genes such as *CHK2*, *BRIP1*, *PALB2* and *ATM* [29–32] have been identified, however, there still remains a proportion of hereditary breast cancer not yet determined. LBC accounts for approximately 10% of all breast cancers compared to the other major histologic subtype, invasive ductal carcinoma (IDC) [33]. Several factors suggest that LBC has a stronger hereditary basis relative to IDC, such as the higher frequency of bilateral disease [33], and also where excess familiality of LBC has been observed in population studies [34]. LBCs compose only 3% and 9% of the breast cancer tumour types seen in germline BRCA 1 and 2 mutation carriers, respectively [35], illustrating that the genetic risk factors for the majority of cases are unaccounted for by these genes.

The histology of LBC is characterized by infiltrative cancer cells which are isolated, highly dispersive and demonstrate a growth pattern with scattered and single files of tumor cells dispersed in stromal tissue [36]. This pathologic appearance is remarkably similar to DGCs and both LBC and DGC demonstrate characteristic mucinous, signet ring cells. This is not unexpected as E-cadherin staining is absent in 85% of sporadic invasive LBC [37] and somatic *CDH1* mutations have been identified in 56% of sporadic LBCs [38]. Furthermore, in IDC, somatic *CDH1* mutations are not found [38] and complete loss of E-cadherin expression is an uncommon feature. As loss of E-cadherin expression is a distinctive trait of both LBCs and DGCs, it likely contributes to the unique histopathologic features shared by the two cancers.

There are some differences with regard to the nature of the mutations seen in LBC and DGC. Generally mutations associated with sporadic LBC have been found to be nonsense or frameshift mutations [39] which encode truncated, non-functional proteins, whereas in sporadic DGC, mutations have generally been found to be splice site and in-frame mutations [11]. In sporadic LBC, mutations in *CDH1* are spread throughout the gene [11] compared with the mutations seen in sporadic DGC which tend to cluster. Germline *CDH1* mutations associated with DGC and/or LBC occur throughout the gene (Fig. 2). However, when the DGC and LBC associated *CDH1* mutations are tabulated and compared based on their 3′ or 5′ positions relative to the halfway point of the *CDH1* coding sequence (1324 or the start of exon 10), LBC associated mutations show a statistically significant trend towards clustering at the 3′ end (Fisher's exact test, two-tailed *P*-value equals 0.0467) (Fig. 2). As this association is of weak statistical significance, it is unlikely to impact clinical testing strategies. Future analyses of novel germline LBC-associated *CDH1* mutations should help to confirm this observation. Another difference between the molecular genetics of the two types of cancers, is that in sporadic LBC, silencing of E-cadherin expression is generally accomplished by a mutation in one allele in combination with loss of heterozygosity (LOH) or promoter hypermethylation in the remaining allele [40]. This is in contrast to sporadic DGC, where biallellic inactivation is achieved by mutations in one allele in concert with promoter hypermethylation in the other [41].

We have recently identified a truncating germline *CDH1* mutation in an LBC family where analysis of the tumour was suggestive of partial LOH in the WT allele [9]. Our current case demonstrates a germline *CDH1* mutation (1565 + 1G > A) in a predominantly breast cancer family, which is predicted to disrupt splicing. The mutation is in the same conserved position as a previously reported mutation (1565 + 1G > T) which was found in an Arabian HDGC family with no recorded history of breast cancer [42]. Moreover, a previous study reported a germline missense mutation in a proband with LBC but did not detail family history, or functionally characterize the missense mutation [43]. These examples demonstrate the need for further studies of germline mutations in LBC families in order to determine the mutation frequency and potential genotype-phenotype correlations.

Lobular breast cancer and HDGC

Breast cancer has been observed in HDGC kindreds to the extent where clustering of LBCs within HDGC families has led to the misclassification of families as breast cancer kindreds who test negative for *BRCA1/2* mutations [4]. In 1998, Keller described the first case of histologically defined LBC in association with HDGC [5]. Since then, several more HDGC families with associated breast cancer were reported where it was observed, that these cases were LBCs when pathology was available [4, 6–8].

Prior to establishment of the association between HDGC and LBC, several efforts to determine whether *CDH1* was a breast cancer susceptibility gene were attempted in view of the well-recognised phenotype of loss of E-cadherin expression displayed by the breast cancer subtype. For various reasons these studies failed to demonstrate the link. Rahman et al. examined 65 cases of lobular carcinoma in situ, however did not pre-screen the cases based on family history and included a wide age range, from 26 to

71 years, not necessarily in keeping with the usual age of onset seen in hereditary cancer syndromes [44]. Salashor examined 19 breast cancer tumours exhibiting LOH at the *CDH1* locus, however of those, only 3 were confirmed to be pure LBC or mixed LBC/IDC pathology [45]. Lei examined 13 familial LBC cases and found no mutations, however did not define the extent of the family history [46].

Penetrance data based on 11 HDGC families, estimated the cumulative risk for LBC for female mutation carriers to be 39% (95% CI, 12–84%) by 80 years of age [47]. More recently we have published an estimated cumulative risk for breast cancer for females by the age of 75 years as being 52% (95% CI, 29–94%) from analysis of 4 predominantly gastric cancer pedigrees from Newfoundland with the 2398delC *CDH1* founder mutation [4]. This is with the caveat that LBC risk for *CDH1* mutation carriers has been assessed within high risk HDGC families, leading to a potential ascertainment bias and underestimation of the role of *CDH1* mutations in LBC development. To accommodate for this we have begun analysis of *CDH1* mutations within familial lobular breast cancer families or those families ascertained through a relatively young index case with confirmed LBC and have found germline *CDH1* mutations in these kindreds [9].

Clinical implications of *CDH1* associated LBC risk

At this time, it seems reasonable to conclude that at least four groups of women are at increased risk for LBC: women with LBC and a family history of breast cancer, women with a known *CDH1* mutation, women from families with diffuse gastric cancer in whom no *CDH1* mutation has yet been identified; and women with a germline *BRCA2* mutation. Since there has not yet been a large population based study of the prevalence of *CDH1* mutations among women with lobular breast cancer, it is premature to recommend genetic evaluation to women with a family history of breast cancer unless, at the very least, one of the breast cancers can be shown to have been lobular. Additional research can be expected to provide better guidance for these families.

Although there are not yet definitive data available on surveillance or risk reduction programs for women with known *CDH1* mutations or untested women from *CDH1*-positive families, the high lifetime risk of LBC (39–52%) [4, 47] that these women face mandates their careful management. We suggest that they follow the recommendations for other high-risk women with hereditary breast cancer predisposition. This subgroup should be advised to practice breast self-examination; and to have annual mammograms, and semiannual clinical breast examination, beginning at least by age 30. There is certainly interest in regular bilateral breast MRI, as lobular breast cancer are known to frequently elude mammographic detection because they do not form masses or develop calcifications. These women can also be counseled to consider hormonal chemoprevention, since most LBCs are estrogen receptor positive [33], and both tamoxifen and raloxifene reduce the risk of estrogen receptor positive [48, 49] breast cancers in randomized trials. In addition, the risk reduction was greatest with both agents in women with lobular carcinoma in situ [50].

Prophylactic mastectomy may also be considered an option by some *CDH1*-positive women, particularly those who have been previously diagnosed with breast cancer in one breast or those who have had to undergo multiple biopsies for abnormal clinical findings. Several studies have reported a 90% reduction in breast cancer incidence with prophylactic mastectomy among women with a strong family history or with a germline BRCA1 or BRCA2 mutation [51, 52]. The published series include some lobular breast cancers, but not at numbers sufficient to permit meaningful subset analysis at this time.

Management of hereditary diffuse gastric cancer

Penetrance studies examining data from HDGC families, have estimated the lifetime risk of developing gastric cancer by age 75 and 80 respectively, to be from 40–67% in men, to 63–83% in women [4, 47]. Although identification of germline *CDH1* mutations has enabled a significant proportion of HDGC families to utilise predictive testing to determine their individual risks of GC within *CDH1* mutation positive pedigrees, unfortunately screening for DGC is ineffective and the current recommendation is for consideration of prophylactic gastrectomy in mutation positive individuals. Positron emission tomography [53] and chromoendoscopic-directed biopsies [54] have been proposed over basic endoscopy as more sensitive means of screening carriers, however screening methods have been consistently undermined by the recurrent discovery of multifocal DGC lesions underlying normal mucosa in prophylactic gastrectomy specimens of individuals with recent negative screening [4, 55, 56]. Regardless of the current limitations of screening, it is currently recommended that consideration for genetic testing and screening begin in at risk individuals in the late teens or early twenties [4] and that prophylactic total gastrectomy be considered in the early twenties for mutation carriers. Female mutation carriers will need specialized counseling to the potential nutritional effects on pregnancy following gastrectomy [57]. Further studies are currently underway to examine the quality of life impact of

prophylactic gastrectomies. In the case report herein, although there was a GC in the maternal grandfather, the family history was more striking for the large number of breast cancer cases. This highlights the particular challenges we currently face with regard to counseling these families which appear to be mainly breast cancer, as it is unknown if the penetrance of DGC in this family is as high as it is in other HDGC pedigrees.

Conclusion

HDGC is one of a number of hereditary cancer syndromes that feature both an increased breast and gastric cancer risk (Table 1). In general, a lack of shared genetic risks for most breast and GI cancers was suggested through a recent study of 13,023 genes in 11 breast and 11 colon cancer cell lines in which the only commonly mutated gene between these two cancer types is *p53* [58]. This likely reflects underlying differences in the biology of these diseases, however also highlights the unique nature of germline mutations in the *CDH1* gene which are strongly associated with specific histologically defined subtypes of breast and GI cancer, namely LBC and DGC which are both part of the HDGC syndrome.

With the recent demonstration of a *CDH1* mutation in a family ascertained through an index case of LBC and in view of the additional new mutation in a predominantly breast cancer family that we have described here, the evidence for establishing LBC as part of the HDGC syndrome is strong. There now is a need for establishing the prevalence of *CDH1* mutations in LBC families to avoid the ascertainment bias generated from only looking at cases from families identified because of their family history of GC. It is not currently known what the risk of GC is in these families which present predominantly as having a susceptibility to breast cancer and therefore identification of *CDH1* as a true susceptibility gene for LBC could result in *CDH1* screening and effective risk reduction strategies for selected breast cancer families and further studies examining their risk for gastric and other cancers.

Most hereditary cancer syndromes are associated with cancer risk involving multiple organs. Here we have discussed germline *CDH1* mutations and the risks with regard to DGC and LBC, however as the recognised spectrum of related cancers broadens, more affected families will be identified and successfully managed with regard to avoidance of specific cancer risks. Longer life expectancy in individuals with penetrant mutations could potentially lead to the development of different, later onset disease as yet to be identified in these kindreds. This represents a particular challenge in hereditary cancer practice as the clinical community tends to be segregated into organ

Table 1 Other syndromes with familial susceptibility to breast and gastric cancers

Syndrome	Mode of inheritance	Associated gene(s)	Sites of primary cancer(s)	Evidence for association with the syndrome
BRCA2 Hereditary Breast/Ovarian Cancer	AD	*BRCA2*	Breast	BC is considered an integral tumor of the syndrome with an average cumulative risk in carriers by age 70 years of 45% (95% confidence interval (CI) 31–56%) [59]
			Ovary	Familial aggregations of both BC and GC have been reported [60]
			Larynx	In a study of 173 families, relative risk for GC was 2.6 [61]
			Prostate	Among Ashkenazi Jewish GC patients, the frequency of 617delT mutation is five times that of the general Ashkenazi Jewish population frequency [62]
				Among other cancers, GC occurred in first degree relatives when mutations were located in the ovarian cancer cluster region of exon 11 of *BRCA2* [63]
BRCA1 Hereditary Breast/Ovarian Cancer	AD	*BRCA1*	Breast	BC is considered an integral tumor of the syndrome with an average cumulative risk in carriers by age 70 years of 72.8% (95% confidence interval [CI] = 67.9% to 77.7%) [64]
			Ovary	
			Prostate	There is a 4 times increased risk for GC [64]
Peutz-Jeghers Syndrome	AD	*STK 11*	Gastrointestinal (GI) tract	GC is considered an integral tumor of the syndrome with a relative risk of 213 (95% confidence interval 96–368) [65]
				BC is considered an integral tumor of the syndrome with a relative risk of 15.2 (95% CI 7.6–27) [65]

Table 1 continued

Syndrome	Mode of inheritance	Associated gene(s)	Sites of primary cancer(s)	Evidence for association with the syndrome
Cowden Syndrome	AD	*PTEN*	Breast	BC is considered an integral tumor of the syndrome with an incidence of 22–50% [66, 67]
			Thyroid	
			Endometrium	GC in situ has been reported in a patient with Cowden Syndrome [68]
Li-Fraumeni Syndrome	AD	*TP53*	Breast	BC is frequently found in families with this cancer susceptibility syndrome [69]
		CHK2	Adrenal cortex	Chompret expanded the spectrum of cancers to include GC [70]
			Connective tissue	Germline *TP53* mutations have been found in GC families without *CDH1* mutations [71–73]
			Kidney	
			Nervous system	The 1100delC *CHK2* allele confers a 2.2 fold risk of BC to carriers [29], however germline mutations in GC kindreds have not been identified [74]
			Pancreas	
			White blood cells	
Familial Adenomatous Polyposis	AD	*APC*	Colon and rectum	Literature review by Shimoyama et al. totalled 30 reported cases of GC and FAP [76]
			Duodenum	
			Thyroid	47% to 49% of primary BCs had promoter hypermethylation at the *APC* locus [77, 78]
			Pancreas	
				23% of LBCs have been shown to have LOH of *APC* [43]
Lynch Syndrome (Hereditary Nonpolyposis Colon Cancer (HNPCC))	AD	*hMSH2*	Colon and rectum	Gastric cancer accounted for 5% of cancers in families harboring *MLH1* or *MSH2* mutations [76]
		hMLH1	Endometrium	
		hMSH6	Stomach	*hMLH1* mutations in large kindred segregated with BCs exhibiting microsatellite instability (MSI) [79]
		hPMS1	Small intestine	
		hPMS2	Urothelium	A slight increased incidence of BC was seen in *hMLH1* mutation carriers [80]
			Kidney	Germline *hMSH2* mutation carrier with BC exhibited LOH for *hMSH2* in tumors analyzed [81]
			Ovary	
			Skin	Analysis of primary invasive BCs demonstrated that 25% of tumours were immunonegative for MSH2 staining [82]
			Pancreas	
			Brain	
			White blood cells	
			Biliary tract	
Ataxia-telangiectasia (AT)	AR	*ATM*	White blood cells	Mutations causing AT in homozygotes, confer susceptibility to BC in heterozygotes, where women with *ATM* mutations have a ~2-fold risk of BC and ~15% of these women will develop the disease [32]
				GC has been reported in association with the syndrome [83–85]
				There is evidence of excess risks of GC in heterozygotes (RR = 3.39, 95% CI = 0.86 to 13.4) [86]

Table 1 continued

Syndrome	Mode of inheritance	Associated gene(s)	Sites of primary cancer(s)	Evidence for association with the syndrome
Xeroderma pigmentosum	AR	*XPA*	Skin	BC and GC have both independently been reported with the syndrome [87,88]
		ERCC3 (XPB)	Eyes	
		XPC		
		ERCC2(XPD)		
		DDB2(XPE)		
		ERCC4(XPF)		
		ERCC5(XPG)		
		POLH(XP-V)		
Werner Syndrome	AR	*WRN*	Connective tissue	GC has been reported in association with the syndrome [89]
			Skin	There are no reports of BC in association with Werner syndrome. Although, there is evidence supporting *WRN* as a low-penetrance familial BC susceptibility gene, where patients harboring both *WRN* Cys1367Arg or *TP53* MspI variants had an increased BC risk (OR = 3.39, 95% CI 1.19–9.71) [90]
			Thyroid	

AD = autosomal dominant, AR = autosomal recessive

specific specialties where as the cancer risks and the risk reduction strategies for germline mutation carriers require a variety of expertise. The medical needs of the HDGC families are therefore best served through an engaged multidisciplinary team.

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