Review Article

Germline mutations in hereditary diffuse gastric cancer

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Abstract

Gastric cancer is one of the leading causes of cancer-related deaths worldwide. Among which, about 1%–3% of gastric cancer patients were characterized by inherited gastric cancer predisposition syndromes, knowing as hereditary diffuse gastric cancer (HDGC). Studies reported that *CDH1* germline mutations are the main cause of HDGC. With the help of rapid development of genetic testing technologies and data analysis tools, more and more researchers focus on seeking candidate susceptibility genes for hereditary cancer syndromes. In addition, National Comprehensive Cancer Network (NCCN) guidelines recommend that the patients of HDGC carrying *CDH1* mutations should undergo prophylactic gastrectomy or routine endoscopic surveillances. Therefore, genetic counseling plays a key role in helping individuals with pathogenic mutations make appropriate risk management plans. Moreover, experienced and professional genetic counselors as well as a systematic multidisciplinary team (MDT) are also required to facilitate the development of genetic counseling and benefit pathogenic mutation carriers who are in need of regular and standardized risk management solutions. In this review, we provided an overview about the germline mutations of several genes identified in HDGC, suggesting that these genes may potentially act as susceptibility genes for this malignant cancer syndrome. Furthermore, we introduced information for prevention, diagnosis and risk management of HDGC. Investigations on key factors that may have effect on risk management decision-making and genetic data collection of more cancer syndrome family pedigrees are required for the development of HDGC therapeutic strategies.

Keywords: *CDH1*; *CTNNA1*; germline mutation; hereditary diffuse gastric cancer; genetic counseling

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Introduction

Gastric cancer is one of the leading causes of cancer-related deaths worldwide. The vast majority of gastric cancers are sporadic. However, approximately 1%–3% of gastric cancers were characterized by inherited gastric cancer predisposition syndromes, knowing as hereditary diffuse gastric cancer (HDGC) (1). Patients diagnosed as HDGC normally have poor prognosis. HDGC is a poorly differentiated adenocarcinoma, especially signet ring carcinoma, mucinous adenocarcinoma and isolated cell-type carcinoma that infiltrates into the stomach wall causing thickening of the wall (linitis plastica) without forming a distinct mass. The average onset age of HDGC

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is 38 years (2).

The diagnostic standards for HDGC was established by the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 (3), which suggested that individuals meet any of the following criteria could be diagnosed as HDGC: "Two or more cases of diffuse gastric cancer (DGC) in first- or second-degree relatives with at least one diagnosed prior the age of 50"; or "Three or more cases of DGC in first- or second-degree relatives, regardless of age of onset". With the development of understanding of HDGC, these criteria were updated by adding two more criteria in 2010 by IGCLC (4), taking individuals with early onset age and lobular breast cancer (LBC) into consideration. In addition, the updated four criteria were also recommended as standards for genetic testing and genetic counseling by National Comprehensive Cancer Network (NCCN) guideline and the American College of Medical Genetics and Genomics (ACMG) as well as the National Society of Genetic Counselors (NSGC) (5), respectively. For the purpose of improving the performance of diagnosis for HDGC, the first two criteria were merged into one in 2015, resulting in the relaxation of restriction on age limit by IGCLC (6). To date, the newly updated criteria are still recommended for diagnosis of HDGC and as standards of sequencing in *CDH1* germline mutations. Therefore, the current well-recognized standards for diagnosis of HDGC and genetic testing for *CDH1* germline mutation consist of the following three criteria: "Two gastric cancer cases in first or second relatives, independent of age, at least one confirmed DGC" ; or "Sporadic DGC prior to age 40"; or "Individuals and families with both DGC and LBC either of which is diagnosed prior to the age of 50 years".

Genetically, HDGC is a rare autosomal dominant inherited gastric cancer syndrome. It has been reported that 25%–30% of families who fulfilled criteria for HDGC were caused by germline alterations in *CDH1* gene (4). In addition, vast majority of individuals inherited a pathogenic variant predisposing to DGC from one parent. Each child of a proband bears a 50% risk of inheriting the cancer-predisposing variant. Moreover, *CDH1* mutation in young individuals with DGC could be potentially from a family with no history of DGC, suggesting the importance of genetic testing for *CDH1* in such population (7). However, in eastern Asian countries, where gastric cancer incidence is relatively high (8), the detection rates for germline *CDH1* mutations are low. Therefore, screenings and genetic testing for HDGC were previously considered not of importance. HDGC is characterized by signet ring carcinoma and considered to be a type of cancer with poor prognosis. Mostly linked with *CDH1* germline mutations, HDGC holds high mortality, whereas LBC is the second most frequent type of carcinoma (9). It is illustrated by Dossus *et al*. that *CDH1* is associated with invasive lobular carcinoma (ILC) (10). The first paper demonstrating the association between breast cancer risk and HDGC was published in 2000 (11,12). In some researchers' view, it is of importance to recognize that HDGC is a syndrome and that LBC can be the first manifestation of this syndrome (13). Therefore, early-onset of LBC could potentially warrant one that considers diagnosis of HDGC.

CDH1 (encoding the cell to cell adhesion protein E-cadherin) germline mutations was found in 30%–50% HDGC patients and the cumulative risk of *CDH1* germline mutation carriers developing gastric cancer by the age of 80 years is approximately 70% for men and 60% for women (14). In addition, female carriers also hold a 39%–52% risk of breast cancer (14), and the association between loss of E-cadherin and ILC was reported by Christgen *et al*. (15). Germline mutations appear to be rare in the countries with high morbidity of sporadic gastric cancer. However, the reason remains unknown. Moreover, *CDH1* Germline mutations have been identified in different ethnic groups (7,16-19). It was postulated that the different genetic background from various ethnicities may have different effects on the viability of embryos that already have one mutated germline *CDH1* allele (20,21). *CDH1* germline alterations encompass small frameshifts, splice-site, nonsense and missense mutations, as well as large rearrangements. Most *CDH1* truncating mutations are pathogenic, and several missense *CDH1* mutations have deleterious effect on E-cadherin function. Truncating alleles of *CDH1* were firstly identified in Maori (indigenous New Zealander) families in which 25 members had died from DGC at young ages, typically at the age of 14–40 years (22). Ongoing studies focused on the assessment of the pathogenicity and penetrance of *CDH1* germline mutations, however, for the majority of HDGC families, the genetic cause remains unknown (23). The investigations of genetic causes other than *CDH1* germline defects were focused on those with strong HDGC family history but without *CDH1* mutations. Recently, germline mutations of some related genes, such as *CTNNA1*, *MAP3K6*, *INSR*, *FBXO24*, *DOT1L MAP3K6*, *CD44*, *PALB2*, *BRCA1*, *RAD51C* and *MET*, have been found to be susceptible for special HDGC family respectively (24,25).

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In this review, we briefly introduced the development of the studies seeking new germline mutations in HDGC, and the new techniques and strategies which spring up before a focused discussion based on most recent data.

Germline mutations in HDGC

CDH1

CDH1 is a tumor suppressor gene located on chromosome 16q22, comprising 16 exons that span 100 kb and encoding E-cadherin protein. E-cadherin is a transmembrane glycoprotein responsible for physical connection of epithelial cells through $Ca^{(2+)}$-binding regions in its extracellular domain, exerting cell-cell adhesion and invasion-suppression functions (26). E-cadherin is critical for the establishment and maintenance of polarized and differentiated epithelia during development (27). It also plays important roles in signal transduction, rearrangement of cells and tissue morphogenesis (28). The activity of E-cadherin in cell adhesion depends on its association with the actin cytoskeleton via undercoat proteins called catenins (α-, β- and γ-) (29,30).

From the first report (22) to date, more than 100 germline mutations of *CDH1* have been reported in families with HDGC (3,26,31-35). The mutations are primarily truncating mutations, usually through frameshift mutations, exon/intron splice site mutations, or single nucleotide variants (3,22,36-39). Moreover, large exonic deletions make up of approximately 4% of these mutations (20). In general, no "hot spots" have been identified and the pathogenic variants have been found distributed throughout the entire gene. Additionally, there are reports on the same pathogenic variant found in several unrelated families, such as c.1003C>T in exon 7 (18,23,31), 1137G>A splicing mutation in exon 8 (18,32,40), c.1901C>T in exon 12 (18,32,41) and a founder mutation 2398delC in four families from Newfoundland, Canada (18). In general, truncating mutations are assumed to be pathogenic, however, clinical management in individuals with missense mutations remains to be elucidated, therefore, both extensive family data and functional data are required for the prediction of pathogenicity caused by a missense mutation (3,38,42). In the absence of such data, it may not be appropriate to use *CDH1* missense mutation to define risks. The pathogenicity of missense mutations can be investigated through *in vitro* analysis, although this is only performed on a research basis (43). For instance, c.1018A>G in *CDH1*, a known disease-causing mutation, was found in a Korean case of pre-symptomatic detection of *CDH1* mutation (44).

CTNNA1

E-cadherin-mediated cell-cell adhesion is affected by 3 cytoplasmic proteins known as α-catenin, β-catenin and γ-catenin. They are identified to work as connectors that anchor E-cadherin to the cytoskeletal actin bundle through cadherin cytoplasmic domain (26). E-cadherin/catenin complex is a powerful inhibitor of invasion. Dysfunction of this adhesion complex causes dissociation of cancer cells from primary tumor nodules, thus possibly contributing to cancer invasion and metastasis (45). As a binding partner of E-cadherin, mutated β-catenin and γ-catenin have been considered as candidates for DGC predisposition (46). Genetic variations of *CTNNA1* have been found to be associated with clinical pathological features. Colorectal cancer (CRC) patients with *CTNNA1* mutation exhibited significantly increased lymph node metastasis (47).

Majewski *et al*. identified a 2 bp germline deletion in exon 2 of *CTNNA1*, which results in a frameshift after Arg27 (p.Arg27Thr.fs*17) using exome sequencing, mass spectrometry genotyping and candidate gene resequencing in a large Dutch HDGC pedigree with no obvious mutation in *CDH1* (24). However, *CTNNA1* protein expression was found lost in tumors from this family. In detail, *CTNNA1* germline truncating allele was presented in two family members with invasive DGC and four in which intramucosal signet ring cells were detected as part of endoscopic surveillance. The remaining *CTNNA1* allele was silenced in the two DGCs from the family that were available for screening, and this was also true for signet ring cells identified in endoscopic biopsies. This suggests that *CTNNA1* may have the potential to be associated with invasiveness of DGC. However, tests in other family pedigrees which fulfilled clinical criteria of HDGC showed that loss of *CTNNA1* was only found in one of ten tumors in *CDH1* wild-type HDGC biopsies (24) . Therefore, evidence from functional studies of *in vitro* and *in vivo* DGC models is required to identify the association between *CTNNA1* and DGC. This was the first report for germline mutation other than *CDH1* in HDGC. Since *CTNNA1* functions in the same complex as E-cadherin, their results called attention to the broader signaling network surrounding these proteins in HDGC (24).

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Other potential candidate susceptibility genes

CDH1 germline mutations were identified in HDGC widely in the European and American countries, with the incidence of greater than 25% (4,14), however, the diagnostic rate in Eastern countries, such as China, was much more lower (data not published). Such discrepancy may attribute to diverse ethnic groups from different regions. Moreover, studies on seeking potential *CTNNA1* germline mutations in HDGC patients without *CDH1* mutation exhibited contradicted results, suggesting that more HDGC family pedigrees may be required or functional studies are needed to further elucidate the association between HDGC and lost function of catenin caused by *CTNNA1* germline mutation. For the uncertainty of pathogenesis in many gastric cancer families linked to cancer predisposition syndromes without *CDH1* germline mutations, it is necessary to continue exploring the potential candidate susceptibility genes of HDGC. Donner *et al*. identified the variants of *INSR*, *FBXO24* and *DOT1L* as new candidates of DGC susceptibility genes in a Finnish HDGC pedigree (25). *INSR* has been shown to affect tumor cell invasion by modulating E-cadherin glycosylation, proposing its potential predisposition in HDGC. Studies indicated that *FBXO24* may lead to malignancies and *DOT1L* has influences on DNA repair, therefore, they may act as new susceptibility genes contributing to HDGC. However, further studies are required to investigate whether there is association between *FBXO24* and *DOT1L* mutations in HDGC (1). In addition, *MAP3K6* is also a newly implicated gene which is associated with gastric cancer and acts as a tumor suppressor gene (1). Gaston *et al*. reported that *MAP3K6* mutation is related to familial gastric cancer (48). *CD44* is a cell surface receptor for hyaluronate, which encodes several protein isoforms. It is reported by da Cunha *et al*. that *CD44* increasingly expressed in malignant lesions including HDGC, and overexpressed when E-cadherin was absent. Therefore, *CD44* was suggested to be a predictable marker for HDGC patients not only carrying *CDH1* mutations but loss of E-cadherin expression (49). Mutations of some genes, such as *PALB2*, *BRCA1* and *RAD51C*, regulating homologous DNA recombination, were detected in HDGC patients with a proportion of 6.5%, whereas mutations in these genes were only found in 2.8% of sporadic gastric cancer patients, reported by Sahasrabudhe *et al*. (50). *MET* gene encodes a protein with an extracellular, transmembrane and a tyrosine kinase domain. The mutation of this gene, previously being reported in patients with hereditary papillary renal carcinoma, was firstly found by Kim *et al*. in a Korean patient with familial gastric cancer (51).

Although new germline mutations are rare and the sample size of some existed studies are too small to draw any conclusions, they warranted further studies to investigate the association of HDGC and other potential gene candidates in addition to *CDH1* in the cohorts of *CDH1* mutation-negative hereditary or familial diffuse gastric cancer (*Table 1*).

Strategies to gastric cancer patients with germline mutations

Patients with *CDH1* mutation may get benefits from endoscopic surveillance to determine the time for surgery (52). NCCN guidelines recommends *CDH1* pathogenic mutation carriers undergo prophylactic gastrectomy, however, individuals who reject such treatment may consider gastroscopic surveillance with multiple biopsies in every 6–12 months of interval after receiving genetic counseling. Additionally, Moreira *et al*. suggested that it is better to distinguish the starting time of surveillance between *CDH1* mutation carriers (at the age of 20 years) and non-carriers (at the age of 40 years) (53). Regarding to the age of receiving prophylactic gastrectomy, NCCN recommends not earlier than 18 years in general, whereas IGCLC suggests the earliest optimal age as 20 years (54). Moreover, Moreira *et al*. and Tan *et al*. expressed the same opinions to IGCLC (53,55). Therefore, albeit different age limit was recommended by NCCN and IGCLC, the international consensus on the earliest age of individuals undertaking prophylactic gastrectomy is not younger than 18 years old. However, van der Post *et al*. advised that one should consider personal status and follow individualized manner to decide when to receive prophylactic gastrectomy (11). Moreover, the appropriate age for genetic testing for patients diagnosed as HDGC is at 18 years of age or earlier (4). Such strategy is also applicable to adolescent asymptomatic *CDH1* mutation carriers. In the report written by Wickremeratne *et al*. (54), a total gastrectomy was performed on a 16-year-old asymptomatic *CDH1* gene mutation carrier, and there were two normal results of gastroscopies with biopsies before the gastrectomy. Family history showed that the patient's mother and aunt died on the age of 39 and 21 respectively, both because of gastric cancer. This case documented the youngest *CDH1* carrier to date, who had a prophylactic gastrectomy, and who was

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Table 1 Genes detected in HDGC and their related information

Genes	Corresponding proteins	Functions	Cancers in which the related genes express	Ref.
CDH1	E-cadherin	Adhesion in cell-cell and tumor suppressor	Gastric cancer (including HDGC); breast cancer; pancreatic ductal adenocarcinoma; colorectal cancer; hepatocellular carcinoma; squamous cell carcinomas of the skin, head and neck; esophageal carcinoma; and melanoma	3,26-44
CTNNA1	Alpha-E-cadherin	Adhesion in cell-cell and tumor suppressor	HDGC, colorectal cancer	24,26,46,47
INSR	Receptor tyrosine kinase	Affect tumor cell invasion	HDGC	25
FBXO24	F-box protein	Lead to malignancies	DGC	1,25
DOT1L	Histone methyltransferase	May has an effect on DNA repair	DGC	1,25
MAP3K6	A serine/threonine protein kinase	As a tumor suppressor	HDGC	1,48
CD44	A cell-surface glycoprotein	Functions in cell-cell interactions, cell adhesion and migration	Hyperplastic polyps, intestinal metaplasia, dysplasia, gastric cancer, gastric cancer (including HDGC)	49
PALB2, BRCA1, RAD51C	Corresponding proteins of their own	Regulate homologous DNA recombination	HDGC, breast cancer	50
MET	A protein with an extracellular, transmembrane and a tyrosine kinase domain	Functions in cellular survival, embryogenesis, and cellular migration and invasion	Hereditary papillary renal carcinoma, family gastric cancer, breast, prostate, ovarian cancers	51

HDGC, hereditary diffuse gastric cancer; DGC, diffuse gastric cancer.

several years younger than the age that guidelines recommended for the consideration of gastrectomy. However, multiple foci of early-stage carcinoma were found in her gastrectomy specimen. In another case, a 43-year-old female accepted genetic counseling and prophylactic total gastrectomy after the death of her brother and nephew (56). Although no evidence of dysplasia or early foci of SRCC was seen in 30 biopsies and 68 postoperative blocks, "prevention is better than cure" was the common consensus and final decision of both patients and families. Study has shown that bigger tumor size and younger age were associated with higher risk of recurrence of gastric cancer (57), therefore, receiving prophylactic gastrectomy at early age is likely to benefit patients with hereditary gastric cancer history and reduce recurrent risk, contributing to longer progression free survival time. In addition, Christgen *et al*. reported that *CDH1* is related to ILC for the loss of E-cadherin, which is evidenced by a conditional knockout mouse model (15). Furthermore, the IGCLC suggests that albeit no DGC family history, patients with sporadic early onset LBCs are strongly recommended to germline screening for *CDH1* especially the one with bilateral sign (9).

Although prophylactic surgery and regular surveillance might have some positive effects on decreasing the mortality rate of HDGCs, the psychological trauma and burden to the germline mutation carriers and their families could not be ignored. Therefore, genetic counseling plays a key role in providing patients and their families with humanistic care in order to facilitate appropriate management to different population. For the individuals who are diagnosed as malignant diseases at young age and/or without cancer family history, genetic counseling may potentially help them decide "the best" risk management strategies, choosing from prophylactic gastrectomy and routine endoscopic surveillances (58). Choi *et al*. reported that an individual with normal physical examination and positive family history obtained benefits from genetic counseling and chose the appropriate strategies for himself and his family members (44). However, decision-making period and process can be different from individuals who are pathogenic mutation

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carriers or at high risks, owing to a number of interrelated factors, such as objective risk confirmation, perceived familial cancer burden, subjective risk perceptions, experiences and perceptions of the different risk management options and life stage, etc. Therefore, the role of genetic counselors is more of importance to guide individuals to understand their risk status followed by making optimal risk management decisions (59). Additionally, guidelines for genetic counseling are also essential to be established to assist medical geneticists, genetic counselors, and other health-care providers in making decisions about appropriate management of genetic concerns (5). Moreover, the establishment of multi-disciplinary team (MDT) consisting of medical geneticists, genetic counselors, clinicians, pathologists, psychologists, etc. is also helpful to assess patients' status in a comprehensive and professional manner, and may support them to make "the most appropriate" risk management decisions.

Molecular genetic testing and perspectives of future research regarding HDGC

Since 50%–70% of the families with HDGC have been reported as no identifiable *CDH1* germline pathogenic variant, it is likely that some of these families may have pathogenic variants in other unidentified HDGC-susceptibility genes. To test *CDH1* and other germline mutations, the following techniques are included: 1) sequence analysis: sequencing detects small intragenic deletions/insertions and missense, nonsense, as well as splice site variants. In general, polymerase chain reaction (PCR) based Sanger sequencing and direct sequencing were commonly applied; and 2) deletion/duplication analysis: exonic or whole-gene deletions/duplications are able to be detected by quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray analysis (CMA) which includes this gene/chromosome segment, such as Sanger sequencing and MLPA (60). PCR-direct sequencing and MLPA was used to evaluate the patients with negative sequencing results (61). Molinaro *et al*. investigated on *CDH1* germline defects in 32 HDGC Italian probands who were selected according to international consensus criteria along with 5 randomly chosen relatives. They used a series of molecular methods to perform genetic testing, including: DNA sequencing, MLPA, single-nucleotide primer extension, bisulfite sequencing, reverse transcription-polymerase chain reaction (RT-PCR), and bioinformatics tools. Their data supported the need of a multi-method approach for *CDH1* genetic testing, demonstrating that both DNA and RNA analyses are required to increase the detection rate of pathogenic mutations, thus reducing the number of patients without a clear molecular diagnosis (34). Another study reported by Majewski *et al*., using exome sequencing, mass spectrometry genotyping and candidate gene resequencing, demonstrated that *CTNNA1* was detected as a HDGC susceptibility gene (24), indicating another classic method for seeking new candidate genes. Recently, a new approach utilizing bio-imaging analysis of *in situ* fluorescence microscopy has gradually arisen to quantify mutant E-cadherin (62). The expression level of E-cadherin was quantified and the distribution of the protein was characterized by a bio-imaging pipeline from *in situ* immunofluorescence images. By virtue of this new approach, the distinction of expressing mutant forms of E-cadherin displaying fluorescence profiles between mutant-type cells and wild-type cells was verified. The study illustrated that this method could be applied in evaluating the pathogenicity of E-cadherin missense variants as a complementary approach. Furthermore, this method could be accepted in detecting a wide range of proteins and some diseases featured by aberrant protein expression or trafficking.

Conclusions

To date, pathogenic *CDH1* germline mutation has been found to be one of the major causes to HDGC, however, individuals carrying such mutation only take one fourth of the total HDGC population. Due to the hereditary susceptible trait, HDGC draws increasing attentions to the identification of pathogenic genes, especially on hotspots, mutation rate and penetrance of relevant germline mutations. With the help of rapid development of cutting edge genetic testing technologies and data analysis tools, genetic testing becomes more efficient and less costly, enabling more researchers to discover candidate susceptibility genes for hereditary cancer syndromes, however, more efforts should be put on family history collection and seeking valuable familial and hereditary cancer syndrome pedigrees. This precious information may potentially play key roles in uncovering new susceptibility genes, improving risk management and providing more choices for individuals carrying pathogenic mutations. Identification of new predisposing genes would give novel

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insights in the molecular pathogenesis of gastric cancer. Furthermore, one should consider difference between ethnic groups and geographical diversity when draft guidelines and standards. New precision medicine techniques like exome sequencing would also provide better tools for predisposing gene screening and early intervention possibilities for the mutation carriers, in addition to development of more reliable surveillance approaches to prevent unnecessary prophylactic gastric resection and to inform joint decision making. The concept of precision medicine was raised to promote individualized therapeutic strategies, and the core ideology of genetic counseling is to make personalized risk management plans which are tailored to specific individual. Genetic counseling for hereditary cancer syndrome including HDGC has met unprecedent opportunity. Studies have shown that decision-making for receiving prophylactic gastrectomy or routine surveillance was influenced by many aspects according to genetic counseling interview data. Thus, more studies on key factors that could have effect on risk management decision-making are required for the improvement of international guidelines and standards. Moreover, experienced and professional genetic counselors as well as a systematic MDT are also required to facilitate the development of genetic counseling and benefit pathogenic mutation carriers who are in need of regular and standardized risk management solutions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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