INTRODUCTION

Germline mutations in E-cadherin (MIM 192,090; CDH1) are associated with autosomal-dominantly inherited cancer syndrome characterized by diffuse gastric cancer, lobular breast cancer, and in some families, cleft lip/palate. However, there may be generations in which these neoplasms do not occur at all in a family and later on, one or another carcinoma arises, which makes it difficult for physicians to think about hereditary origin.

Methods: We report the first Mexican family with CDH1 mutation (variant c.377del).

Results: An asymptomatic young woman underwent a search for mutations in susceptibility genes for breast cancer due to the history of this neoplasm in her mother and maternal aunt. A CDH1 mutation was detected. After an endoscopy, a diffuse gastric carcinoma was found. Later on, three generations of this family were studied. The findings are presented.

Conclusion: Medical communities should be aware of the contribution of this gene in the development of hereditary diffuse gastric carcinoma (HDGC) and breast cancer.

KEYWORDS
breast carcinoma, CDH1 gene, gastric carcinoma, Mexican family
patients have HDGC whose main cause is a germline mutation in the \textit{CDH1} gene in 30\%–50\% of cases (Fitzgerald et al., 2010). There are at least 100 different germline mutations of \textit{CDH1}, especially frameshift mutations that cause a truncated protein; also exon/intron splice site mutations and single nucleotide mutations have been described. Large exonic deletions account for 4\% of these mutations (Fitzgerald et al., 2010). Although there is a study about E-cadherin expression in sporadic gastric cancer from Mexico (Gamboa-Dominguez et al., 2015), there are no reports of families with germline mutations in this gene. We report the first Mexican family with \textit{CDH1} mutation in which three generations are studied.

2 | MATERIAL AND METHODS

Editorial Policies and Ethical Considerations: The study was approved by the Ethics Committee and the participants signed an informed consent.

2.1 | Family report

A 35-year-old woman underwent multigene panel testing in genes associated with BC due to the history of this neoplasm in her mother and a maternal aunt who presented the tumor at 55 and 50 years of age, respectively. The study ruled out mutations in the following genes: \textit{BRCA1} (MIM 113705), \textit{BRCA2} (MIM 600185), \textit{TP53} (MIM 191170), \textit{PTEN} (MIM 601728), and \textit{STK11} (MIM 602216); however, the variant c.377delC [NM_004360.5(\textit{CDH1}):c.377del (p.Pro126Argfs* 89); LOVD, Genomic variant #0000058778; individual ID 00032542] in heterozygous state within the sequence of the \textit{CDH1} gene (HGNC:1748; LRG_301t1; ENSG00000039068.19) was identified (Figure 1). The young woman underwent a gastric endoscopy that showed no macroscopic alterations, however, the biopsies showed an undifferentiated diffuse adenocarcinoma with signet-ring cells. The patient underwent a total gastrectomy and Roux-en-Y esophagojejunostomy. The definitive histopathological study confirmed the presence of intramucosal early gastric adenocarcinoma. Given the molecular findings, other members of the family were analyzed for this specific mutation. The results are shown in Figure 2.

The patient had several postoperative complications including transient dysphagia and esophageal stenosis that required dilatations. The relatives carrying the mutation are for the time being in endoscopic follow-up with annual gastric biopsies; breast MRI and breast ultrasound are performed in those women under 40 years of age.

3 | DISCUSSION

Since the first report of \textit{CDH1} germline mutations in a Maori population from New Zealand with a strong cluster for gastric tumors (Jones, 1964), more information about this gene has been collected. Later on, the association of gastric cancer and lobular breast carcinoma in families with mutations in the \textit{CDH1} gene was reported (Keller et al., 1999). Therefore, these two entities have been part of the HDGC syndrome (Corso et al., 2018). However, there may be generations in which these neoplasms do not occur at all, in the same family and, later on, one type or another of neoplasm arises, which makes it difficult for physicians to think about the possibility of a hereditary case. Such is the situation of the family reported. The index case of gastric carcinoma, a young woman, 35 years old, was screened for mutations due to a history of BC in her mother and aunt who presented the neoplasm between 50 and 55 years of age. After the finding of the mutation, the mother, one sister, two aunts, two cousins, and the maternal grandmother were tracked for the mutation. The maternal great-grandfather had died from a DGC with signet ring cells at 55 years of age. Initially, in this man it was considered that having blood group A and being a heavy smoker had contributed to the development of cancer. However, in retrospect it was evident that the mutation in the index case came from the mother’s line. It calls the attention that the maternal grandmother (mutation carrier) died at 93 years of age due to cardiac involvement and the development of neoplasia was never documented. Her last

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{CDH1_c377del.png}
\caption{Partial electropherogram of \textit{CDH1} gene sequencing (HGNC:1748; LRG_301t1; ENSG0000039068.19). The arrow shows affectation on the reading frame sequence in the allele affected by variant c.377del (p.Pro126Argfs * 89)}
\end{figure}
mammography, at 85 years old of age, showed a fatty mammary pattern, BIRADS 1. The two confirmed BC cases were a lobular carcinoma and a moderately differentiated ductal carcinoma, both with positive estrogen and progesterone receptors; they had a bilateral mastectomy and chemotherapy and are currently asymptomatic.

With CDH1 mutations, the cumulative risk of developing DGC by age 80 is 70 and 56% in men and women, respectively. The cumulative risk for lobular BC is of 42% in women by age 80 (Hansford et al., 2015). In the other hand, somatic CDH1 mutations are detected in 10%–56% of lobular BC and in 5% of ductal carcinomas (Lei et al., 2002).

In Western medicine there seems to be consensus about prophylactic total gastrectomy in patients with germline mutation in the CDH1 gene; surgery is usually performed in 18- to 40-year-old carriers (van der Post et al., 2015). Foci of intramucosal signet ring cell carcinomas have been observed in 80%–83% of the resected stomachs (Gjyshi et al., 2018; Pantelis et al., 2018), even in patients of 14 years of age (Gullo et al., 2018). However, prophylactic total gastrectomy has considerable morbidity and functional consequences. Understanding the pathophysiology of the damage produced by mutations would help to propose new treatments.

Human E-cadherin is a 120-kDa transmembrane glycoprotein; the extracellular component has five repeat domains with four calcium-binding sites that are important in stabilization of the conformation; the membrane component connects the extracellular part of E-cadherin to the cytoplasmic part, containing the recognition sites for catenins (Kellen, 1996). This cytoplasmic part binds to beta- or gamma-catenin and to p120cas, and also to alpha-catenin. Alpha-catenin forms the link with α-actinin and F-actin.

The downregulation of E-cadherin in malignant mammary cells is associated with expression of vimentin for invasion to occur. Experimental studies have shown that tamoxifen activates the E-cadherin/catenin complex. In fact, insulin-like growth factor 1, retinoic acid, and the citrus flavonoid tangeretin can activate the E-cadherin/catenin complex (Kellen, 1996) and this complex could be a therapeutic target.

In the case of families with hereditary DGC, germline mutations of CDH1 gene occur in 30% of the cases; of these, 23% are missense mutations. Truncating CDH1 mutations are the majority of CDH1 germline variants followed by missense variants, and variants affecting splice sites [Kellen, 1996]. Mutations affect each of the 16 exons of the gene, with some hotspots for truncating mutations c.1003C>T, c.1212delC, c.1137G>A, 1792C>T, or 2398delC [Li, Lo, & Rudloff, 2018].

Mutations in CDH1 gene also may be associated with colon cancer. In fact, when 1,000 patients with advanced cancer were studied using exome sequencing of a 202-gene panel, 151 patients showed germline variants and 15 patients had pathogenic germline variants, including two cases with CDH1 mutations (You et al., 2019). It is reported that families with truncating variants in the PREPRO region have an increased probability of colorectal cancer, when compared with variants in other regions (Lo et al., 2019).

In the other hand, somatic mutations occur in both sporadic and hereditary forms. In case of HDGC not associated with CDH1 germline mutations, promoter hypermethylation has been described in 50% of patients (Corso et al., 2013). The methylation status in subjects with mutations in
the germline of the CDH1 gene could also contribute to explain the phenotypic variability in the different generations.

It is logical to think that mutations affecting different E-cadherin protein domains have distinct effects in motility. Experiments in cell lines with different CDH1 missense mutations localized on the extracellular and juxtamembrane domains, both affecting the integrity of the extracellular domain, led to increased cell motility accompanied by increased epidermal growth factor receptor (EGFR) activation, and also increased activation of Src kinase and p38 mitogen-activated protein kinases (MAPK). In this type of mutations there seems to be a genotype–phenotype correlation that defines a subset of HDGC cases which may benefit from EGFR inhibitors (Mateus et al., 2009).

Experiments with cancer rat model using NMU (N-nitrosodimethylurea) as carcinogen had shown that 9-cis-isomer of retinoic acid (9cRA) is effective for preventing mammary cancer and enhances the chemopreventive activity of low doses of tamoxifen, increasing expression of E-cadherine, at cell–cell contact sites in BC cells. These results suggest that retinoids and tamoxifen may be useful not only in the prevention of breast cancer but also in its treatment (Anzano et al., 1994).

The recommended prophylactic treatment for carriers of germline mutations in the CDH1 gene is total gastrectomy (van der Post et al., 2015; Strong et al., 2017); bloc resection of gastric mucosa in early carcinoma is an accepted treatment in those patients who are not carriers of mutations, however, it is not enough in patients with germline mutations as the neoplasm can develop anywhere in the mucosa. Perfecting techniques like mucosal (EMR) and endoscopic submucosal dissection (ESD) combined with new hemostatic agents for exudative hemorrhages from small vessels in the gastrointestinal tract could be an option (Subramaniam, Kandiah, Thayalasekaran, Longcroft-Wheaton, & Bhandari, 2019).

Medical communities should be aware of the contribution of this gene in the development of gastric carcinoma, mammary carcinoma, and occasionally colon cancer.

CONFLICTS OF INTEREST
The authors declare that there are no conflicts of interest.

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