Clinical Characteristics of Lobular Breast Carcinoma in CDH1 genetic predisposition. Experience from the Institut Curie.

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LAY ABSTRACT

Hereditary diffuse gastric cancer (HDGC) and hereditary lobular breast cancer (HLBC) may be linked to a rare genetic predisposition due to germline pathogenic variants (PV) of the *CDH1* gene. We will review the criteria that should lead us to consider this type of hereditary predisposition on the basis of personal characteristics and/or family history. It is important to identify the rare families affected by this type of hereditary predisposition, in order to adapt surveillance and management.

BACKGROUND

HDGC and HLBC may be linked to monoallelic germline pathogenic variants (PV) or likely pathogenic variant (LPV) of the *CDH1* gene. *CDH1* genetic testing is recommended in patients fulfilling either family or individual criteria. More recently, the inclusion of the *CDH1* gene in the HBOC panel has identified families whose history was less suggestive than before. In this context, risks estimates, genomic characteristics underlying gastric and breast tumorigenesis are still poorly characterized and need to be consolidated.

OBJECTIVES

To specify the criteria for the indication of constitutional analysis that may identify a hereditary genetic predisposition to *CDH1* and to recall the methods of surveillance and management in this context.
To describe PV, clinico-pathological characteristics and outcome of breast cancers diagnosed in this context.

METHODS

The criteria used were a constitutional genetic analysis carried out at the Institut Curie, Paris, and available histological and follow-up data. Cases will be retrospectively reviewed and E-cadherin loss of expression analyzed.
Between 2008 and July 2023, we identified 17 women breast cancer affected and carrier of a *CDH1* PV.

RESULTS

The main clinical, familial and follow-up data of the 17 patients are presented in Table 1.
CDH1 genetic status was identified at or after the diagnosis of breast cancer on the basis of personal and family criteria.
No developmental abnormalities such as dental agenesis or cleft lip and palate were observed in these patients or their family members.

Table 1	N = 17	Range
Median age at first diagnosis	49,7	27-76
Metastasis at diagnosis Metastasis after diagnosis	1 2	
DGC prior breast cancer	2	
Controlateral breast cancer	7	
Bilateral mastectomy	4	18 months – 14 years

The descriptions of the VPs identified are shown in the diagram in Figure 1. Constitutional mutations are distributed across all genes (precursor, extra-cellular domain and cyto-domain). The majority of patients have truncating variants. No correlation was found between genotypes and phenotypes.

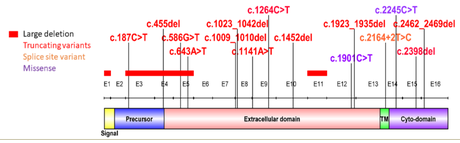

Figure 1. Lollipop plot illustrating all CDH1 variants in our cohort (N=17).

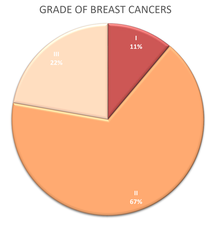

Figure 2. Pie chart showing the grade level of breast cancers in patients carrying a pathogenic alteration of the CDH1 gene (N=18).

Grade I : n = 2/18. Grade II : n= 12/18. Grade III : n = 4/18.

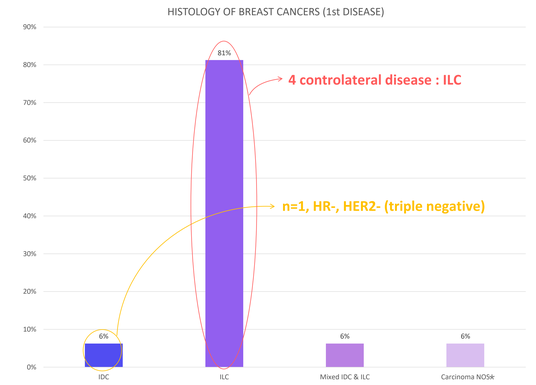

Figure 3. Histogram showing the histology of breast cancers in patients carrying a pathogenic alteration of the CDH1 gene (N=16).

IDC : Invasive Ductal Carcinoma (n=1/16).
ILC : Invasive Lobular Carcinoma (n=13/16).
Mixed IDC & ILC (n=1/16).
*carcinoma without indication of histological type reported with family history of ILC (n=1/16).

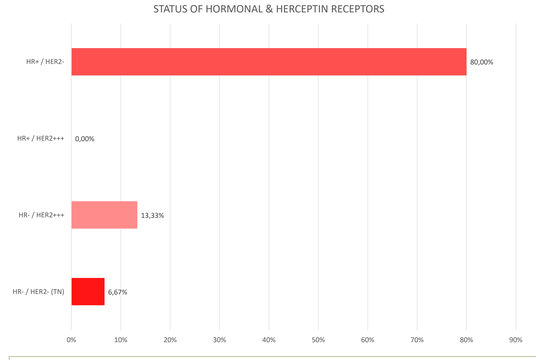

Figure 4. Histogram representing positivity or the negativity of hormonal receptors (HR) and Herceptin receptors (HER2) of breast cancers in patients carrying a pathogenic alteration of the CDH1 gene (N=10).

HR : Hormonal Receptors (Estrogen and Progesterone). HER2 : Herceptin Receptor.
The majority of breast cancers are positive for HR but negative for the HER2.
identical to what is observed in sporadic ILC.
One is both negative for HR and HER2 (it is also the only one IDC). This patient developed breast cancer at less than 30 years of age and carrying a LPV of the *CDH1* gene. This LPV was identified in a multigene panel analysis, and is currently being investigated to determine its involvement in the development of this breast cancer.

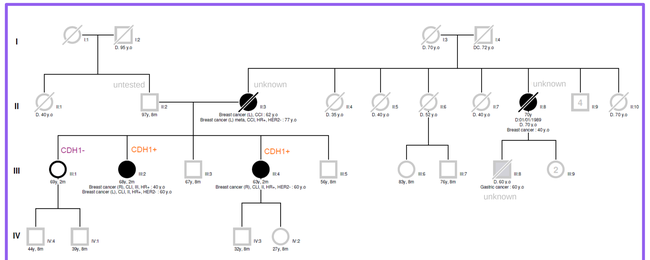

Figure 5. Genealogical tree of family in which a pathogenic alteration of the CDH1 gene has been identified.
Two sisters with ILC (HR+, HER2-) at ages 40 and 60. Their mother and a maternal aunt had breast cancer at ages 62 and ipsilateral relapse at 77 years old and 40 years old for the maternal aunt. One case of gastric cancer. The father was untested. The suspected hereditary branch is maternal but family members are not yet involved in genetic testing.

CONCLUSION

2020 HDGC genetic testing criteria (1)
Family criteria
≥2 cases of gastric cancer in family regardless of age, with at least one DGC (Diffuse Gastric Cancer)
≥1 case of DGC at any age and ≥1 case of LBC (Lobular Breast Cancer) <70yrs in different family members
≥2 cases of LBC in family members <50yrs
Individual criteria
DGC <50yrs
DGC at any age in individuals of Māori ethnicity
DGC at any age in individuals with a personal or family history (1st degree) of cleft lip/cleft palate
History of DGC and LBC, both diagnosed <70yrs
Bilateral LBC, diagnosed <70yrs
Gastric *in situ* signet ring cells and/or pagetoid spread of signet ring cells in individuals <50yrs

- The lifetime risk of ILC among *CDH1* pathogenic variant female carriers has been reported to be between 39% and 42%. In addition to gastric management, breast screening recommendations endorse annual mammogram and breast MRI starting at age 30 years. Preventive breast surgery may also be discussed on a case-by-case basis in this context.
- Our preliminary data suggest that ILC have the same characteristics as sporadic ILC, apart from age at diagnosis.
- Impact on prognosis still to be determined.
- With the implementation of multigene panel analysis, *CDH1* PV/LPVs are being identified more frequently in families that do not fulfil the 2020 HDGC criteria. The challenge of a better understanding of tumors risks and adequate monitoring is still relevant.

REREFENCES

1, Hereditary Diffuse Gastric Cancer: Updated Clinical Practice Guidelines. *Lancet Oncol* 2020. Blair, V and al.
Genotype-first approach to identify associations between *CDH1* germline variants and cancer phenotypes: a multicentre study by the European Reference Network on Genetic Tumour Risk Syndromes