Hereditary diffuse gastric cancer syndrome: improved performances of the 2015 testing criteria for the identification of probands with a CDH1 germline mutation

Patrick R Benusiglio, Chystelle Colas, Etienne Rouleau, Nancy Uhrhammer, Pierre Romero, Audrey Remenieras, Jessica Moretta, Qing Wang, Antoine de Pauw, Bruno Buecher, et al.

► To cite this version:

Patrick R Benusiglio, Chystelle Colas, Etienne Rouleau, Nancy Uhrhammer, Pierre Romero, et al.. Hereditary diffuse gastric cancer syndrome: improved performances of the 2015 testing criteria for the identification of probands with a CDH1 germline mutation. *Journal of Medical Genetics*, 2015, 52 (8), pp.563-565. 10.1136/jmedgenet-2015-103153 . hal-01647109

HAL Id: hal-01647109

<https://hal.science/hal-01647109>

Submitted on 11 Jan 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Communication

Hereditary Diffuse Gastric Cancer syndrome: improved performance of the 2015 testing criteria for the identification of probands with a germline *CDH1* mutation.

Patrick R Benusiglio ¹, Chystelle Colas ², Etienne Rouleau ³, Nancy Uhrhammer ⁴, Pierre Romero ⁴, Audrey Remenieras ⁵, Jessica Moretta ⁶, Qing Wang ⁷, Antoine De Pauw ³, Bruno Buecher ³, Dominique Stoppa-Lyonnet ^{3,8}, Emmanuelle Mouret-Fourme ³, Catherine Noguès ³, Marina Di Maria ¹, Camille Tlemsani ⁹, Mathilde Warcoin ², Sophie Grandjouan ¹⁰, David Malka ¹, Olivier Caron ¹, Martine Blayau ¹⁴.

1- Consultation d'Oncogénétique, Département de Médecine Oncologique, Gustave Roussy Cancer Campus, Villejuif, France.

2- Centre de Génétique Moléculaire et Chromosomique, Centre Hospitalier Universitaire Pitié-Salpêtrière AP-HP, Paris, France.

3- Consultation et Laboratoire d'Oncogénétique, Institut Curie, Paris et Saint-Cloud, France.

4- Laboratoire de Diagnostic Génétique et Moléculaire, Centre Jean Perrin, Clermont-Ferrand, France.

5- Oncogénétique Moléculaire, CLCC Institut Paoli-Calmettes, Marseille, France.

6- Département d'Anticipation et de Suivi du Cancer, CLCC Institut Paoli-Calmettes, Marseille, France.

7- Plateforme de Génétique Constitutionnelle, Centre Léon Bérard, Lyon, France.

8- Université Paris-Descartes, Sorbonne Paris Cité, Paris, France.

9- Service d'Oncologie, Centre Hospitalier Universitaire Cochin AP-HP, Paris, France.

10- Consultation d'Oncogénétique, Centre Hospitalier Universitaire Cochin AP-HP, Paris, France.

11- Service de Génétique Moléculaire et Génomique, Centre Hospitalier Universitaire de Rennes, Rennes, France.

1
2 The international consensus testing criteria for germline *CDHI* mutations were recently
3 revised in order to increase their performance, in particular their sensitivity. It is paramount to
4 identify a high proportion of actual mutation carriers, as finding a mutation in a proband and
5 subsequent testing of relatives allows for risk-reducing measures regarding diffuse gastric
6 cancer (DGC) and lobular breast cancer (LBC). We collected data on all French probands
7 tested for *CDHI* in a retrospective study on Hereditary DGC syndrome (HDGC). Out of 627
8 probands, 52 were mutation carriers. We compared the new 2015 version of testing criteria to
9 the 2010 version, and showed that both the sensitivity and the Youden index *J*, which
10 estimates the discriminating power of the criteria, increased.

11 *CDHI* is a tumour suppressor gene located on chromosome 16q22. It codes for the E-cadherin
12 adhesion protein. Monoallelic germline mutations in *CDHI* cause HDGC, in which carriers
13 have a high lifetime risk of DGC (also called signet ring cell gastric cancer), and LBC
14 (reviewed in 1). In clinical practice, mutations are first identified in a proband with a personal
15 history of DGC and/or LBC, and adult relatives are subsequently tested to see whether they
16 also carry the mutation. Asymptomatic carriers are then advised to undergo risk-reducing
17 gastrectomy, and for females annual breast cancer screening using MRI.

18 The International Gastric Cancer Linkage Consortium defined clinical criteria warranting
19 *CDHI* germline testing in a proband. The criteria were first published in 1999 and then
20 updated in 2010 (2,3). A new 2015 version is being published in this issue of the Journal of
21 Medical Genetics (4). Its aims are improvements in sensitivity and clarity through the removal
22 of the 50 year-old age threshold for families with two cases of DGC, the merger of the first
23 two 2010 criteria into a single, simpler one, and the integration of recent developments in the
24 field, most notably the identification of mutations in cases with bilateral LBC at a young age
25 but no personal or family history of DGC (table 1) (5,6). The objective of our study was to
26 compare the performances of the 2010 and 2015 criteria, and more specifically to estimate the
27 changes in sensitivity between the two versions.

28 We collected retrospective clinical and molecular data on all unrelated probands tested for
29 *CDHI* germline mutations in France as of 1 July 2014. The decision to test belonged to the
30 prescribing physician and the laboratory to which DNA was sent, and consensual criteria in
31 place at the time did not have to be met. All probands had to sign an informed consent form
32 before genetic testing could be prescribed. Gene analysis was performed on circulating blood

leucocytes in six accredited laboratories using Sanger sequencing and in the majority of cases, multiplex ligation probe-dependant amplification (MLPA). Some cases were not analyzed by MLPA because the technique had not yet been implemented in the laboratory in charge of the sample, and the clinical context (i.e. low probability of a genetic abnormality) did not justify referral to another better-equipped laboratory. Frameshift, nonsense and splice-site mutations, missense variants reported as deleterious in the literature, and large gene rearrangements were considered deleterious (7). Statistics were calculated using R software (<http://www.r-project.org/>, version 3.1.2). The two exploratory 2015 criteria addressing testing in patients with a personal or family history of cleft lip/palate or with *in situ*/pagetoid spread signet ring cells were excluded from this work as data were unavailable.

The total number of tested probands was 627, 52 of whom (8%) carried a *CDHI* mutation. We then restricted our analyses to probands fulfilling the 2010 and 2015 testing criteria (table 1). One hundred and seventy-six probands met the 2010 criteria, of whom 35 were mutation carriers. Sensitivity, specificity, positive predictive value (PPV, corresponding to the mutation detection rate) and negative predictive value (NPV) were 0.69 (95% CI 0.56-0.81), 0.76 (95% CI 0.72-0.79), 0.21 (95% CI 0.15-0.27), and 0.96 (95% CI 0.94-0.97) respectively (table 2). The 2015 criteria were met by 216 probands, 41 of whom carried a mutation, and the sensitivity, specificity, PPV and NPV were respectively 0.81 (95% CI 0.71-0.91), 0.70 (95% CI 0.66-0.74), 0.20 (95% CI 0.14-0.25) and 0.98 (95% CI 0.97-0.99) (tables 1 and 2). The Youden index (*J*), a statistic that determines the optimal cut-off point for a test (in this context, perform vs. do not perform *CDHI* germline testing) whose outcome is binary (mutation vs. no mutation), and therefore summarizes its discriminating power, increased from 0.45 to 0.51 between 2010 and 2015 (8).

There were 36 distinct point mutations (8 nonsense, 15 frameshift, 3 deleterious missense, 10 splice-site) and four distinct large rearrangements in the 52 carriers (supplementary table 1). There was no apparent genotype-phenotype correlation (data not shown).

Testing criteria defined by experts are important, as they help clinical and laboratory-based cancer geneticists determine who should and should not be tested for germline mutations. They need to be sensitive enough to ensure that most mutation carriers are identified and then managed accordingly, but not at the expense of too much specificity as to avoid unnecessary and resource-consuming testing of individuals unlikely to carry mutations. In HDGC, high sensitivity is paramount. Indeed, *CDHI* mutation carriers have a lifetime risk of DGC and

LBC (in females) of 70% and 42% respectively (7), and the identification of a mutation in a proband, and subsequently in his relatives, leads to risk-reducing and screening recommendations such as prophylactic gastrectomy and annual breast MRI. In the revised 2015 criteria, the merger of the first two 2010 criteria into a single simpler one with no age limit, and the addition of the multiple early-onset LBC with no DGC criterion led to the testing of 40 additional probands, six of whom (15%) carried a mutation, and to increased sensitivity (0.81 vs. 0.69). The 2010 and 2015 confidence intervals for sensitivity did overlap, but significance would be extremely difficult to achieve in a comparison of two sets of closely-associated criteria. Specificity declined, as expected when test indications are expanded. PPV was unchanged, while NPV increased significantly. Overall the new criteria have improved discriminating power, as illustrated by the increased Youden index (0.51 vs. 0.45).

In our large series of 627 probands, 411 did not meet any consensual testing criteria. Detection rate was unexpectedly high (15%) in probands with sporadic DGC $\geq$ 40 years (table 1), while only 3% of unselected probands with LBC were carriers. As for the 259 remaining probands, the vast majority had gastric cancer of undetermined or intestinal histology or ductal breast cancer, and only two mutations were found: in a proband with a personal history of signet ring cell cancer of the rectum, and in an unaffected proband with two relatives with GC of unknown type. *CDHI* germline mutations are specifically associated with DGC and LBC, and our study is a welcome reminder that one should not offer *CDHI* testing to patients with other gastric and breast cancer histologies.

Conflicts of interest

The authors have no conflicts of interest to report.

Contributions

Design of the study: PRB, ER, OC, MB.

Genetic counselling and clinical management of patients: PRB, CC, JM, ADP, BB, DSL, EMF, CN, MDM, MW, SG, DM, OC.

Gene analysis: CC, ER, NU, AR, QW, MB.

Data collection: PRB, CC, ER, NU, PR, AR, QW, ADP, CT, MW, MB.

Data analysis and interpretation: PRB, EMF.

Drafting of the manuscript: PRB.

1 Critical review and approval of the manuscript: all authors.

2 Guarantor:

PRB.

2010 testing criteria	Index cases	CDH1 mutation	Detection rate
1. Three DGC in family, regardless of age, at least one confirmed DGC	30	8	27%
2. Two DGC in family, one of them < age 50, at least one confirmed DGC	31	12	39%
3. Sporadic DGC < 40	103	10	10%
4. Personal or family history of DGC and LBC, one diagnosis < 50	12	5	42%
Total (criteria met)	176	35	20%
Total (consensus criteria not met)	451	17	4%
Total (all probands)	627	52	8%
2015 testing criteria			
<i>Established criteria</i>			
1. Two GC cases regardless of age, at least one confirmed DGC	79	22	28%
2. Sporadic DGC < 40	103	10	10%
3. Personal or family history of DGC and LBC, one diagnosis < 50	12	5	42%
<i>Exploratory criteria</i>			
4. Bilateral LBC or family history of ≥ 2 LBC, all < 50	22	4	18%
Total (criteria met)	216	41	19%
Sporadic DGC ≥ 40	39	6	15%
LBC outside criterion 4	113	3	3%
Other	259	2	1%
Total (consensus criteria not met)	411	11	3%
Total (all probands)	627	52	8%

Table 1. 2010 and 2015 consensus testing criteria and mutation detection rate in all French probands tested for *CDH1* germline mutations. DGC, diffuse gastric cancer. LBC, lobular breast cancer. Family history in 1st and 2nd degree relatives must be taken into account.

	2010	2015
Sensitivity (95%CI)	0.69 (0.56-0.81)	0.81 (0.71-0.91)
Specificity (95%CI)	0.76 (0.72-0.79)	0.70 (0.66-0.74)
PPV (95%CI)	0.21 (0.15-0.27)	0.20 (0.14-0.25)
NPV(95%CI)	0.96 (0.94-0.97)	0.98 (0.97-0.99)
<i>J</i>	0.45	0.51

Table 2. Comparison of test statistics between the 2010 and 2015 consensus criteria for *CDH1* germline mutation testing. *J*, Youden index. NPV, negative predictive value. PPV, positive predictive value.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27

REFERENCES

1. Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. *Lancet Oncol.* 2015 Feb;16(2):e60-e70.

2. Caldas C, Carneiro F, Lynch HT, Yokota J, Wiesner GL, Powell SM, Lewis FR, Huntsman DG, Pharoah PD, Jankowski JA, MacLeod P, Vogelsang H, Keller G, Park KG, Richards FM, Maher ER, Gayther SA, Oliveira C, Grehan N, Wight D, Seruca R, Roviello F, Ponder BA, Jackson CE. Familial gastric cancer: overview and guidelines for management. *J Med Genet.* 1999 Dec;36(12):873-80.

3. Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, Chung DC, Norton J, Ragunath K, Van Krieken JH, Dwerryhouse S, Caldas C; International Gastric Cancer Linkage Consortium. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet.* 2010 Jul;47(7):436-44.

4. Van der Post RS *et al.* Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet.* In Press.

5. Benusiglio PR, Malka D, Rouleau E, De Pauw A, Buecher B, Noguès C, Fourme E, Colas C, Coulet F, Warcoin M, Grandjouan S, Sezeur A, Laurent-Puig P, Molière D, Tlemsani C, Di Maria M, Byrde V, Delaloge S, Blayau M, Caron O. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. *J Med Genet.* 2013 Jul;50(7):486-9.

6. Petridis C, Shinomiya I, Kohut K, Gorman P, Caneppele M, Shah V, Troy M, Pinder SE, Hanby A, Tomlinson I, Trembath RC, Roylance R, Simpson MA, Sawyer EJ. Germline CDH1 mutations in bilateral lobular carcinoma in situ. *Br J Cancer.* 2014 Feb 18;110(4):1053-7.

7. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol.* Published online February 12, 2015. doi:10.1001/jamaoncol.2014.168.

8. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. *Acta Paediatr.* 2007 May;96(5):644-7.