

Hereditary diffuse gastric cancer and genetic syndromes of stomach cancer: What clinicians need to know

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FMUP/CHSJ



Gastric cancer

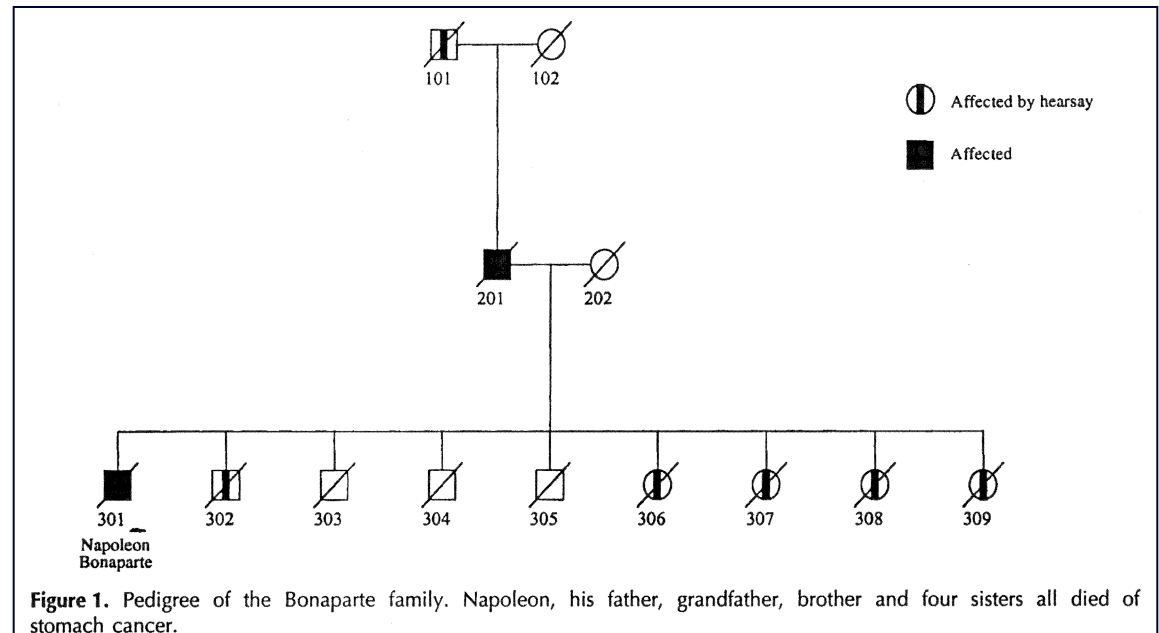
Sporadic cancer
(90%)

Familial cancer
(10%)

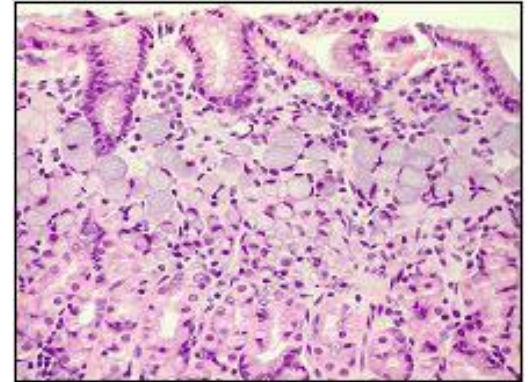
- Familial Gastric Cancer (FGC)
- Familial Intestinal Gastric Cancer (FIGC)
- Familial Diffuse Gastric Cancer (FDGC)

Hereditary cancer
(1-3%)

Familial (hereditary?) Gastric Cancer



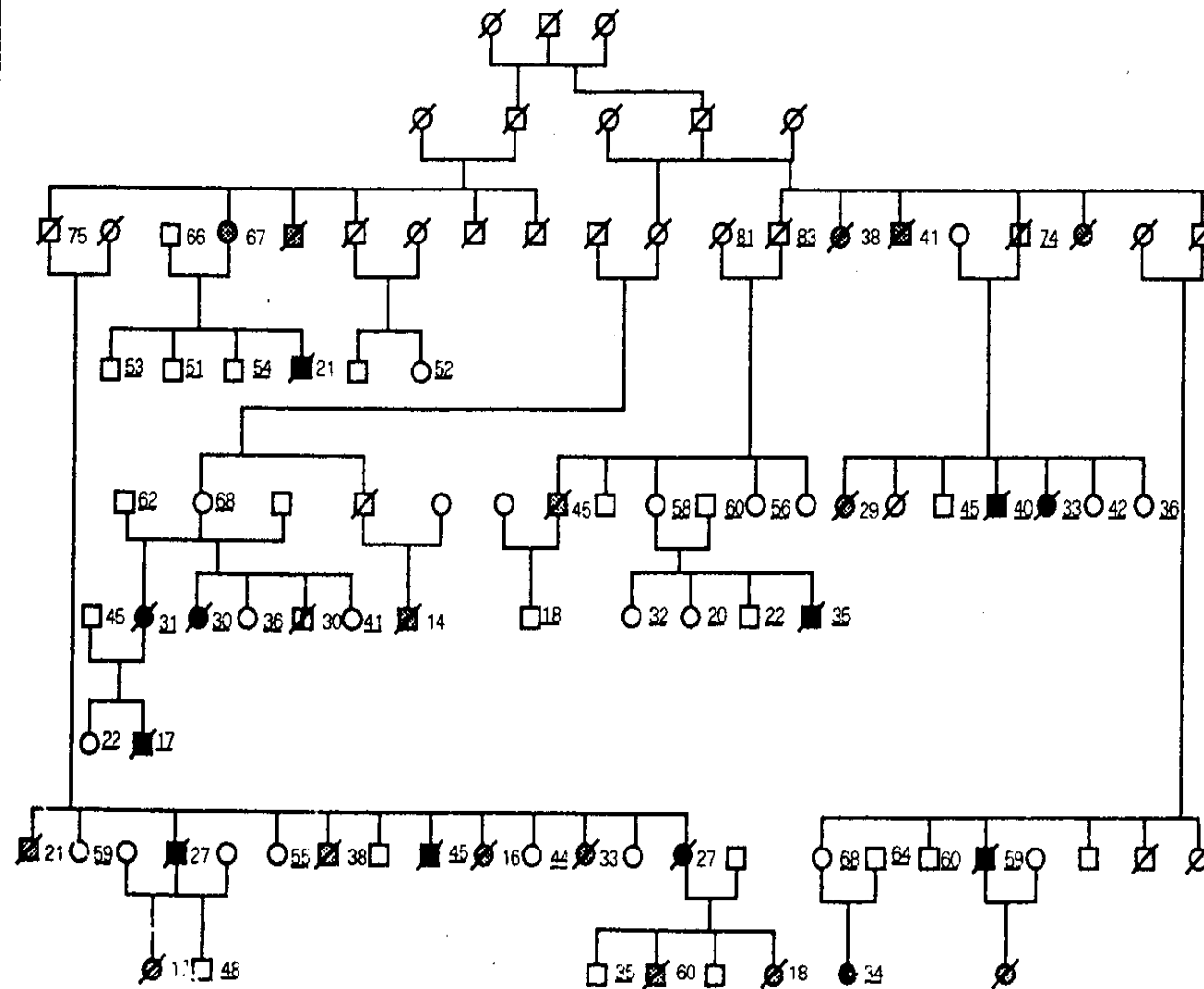
Maori kindred



E-cadherin gene
(*CDH1*)*germline
mutations



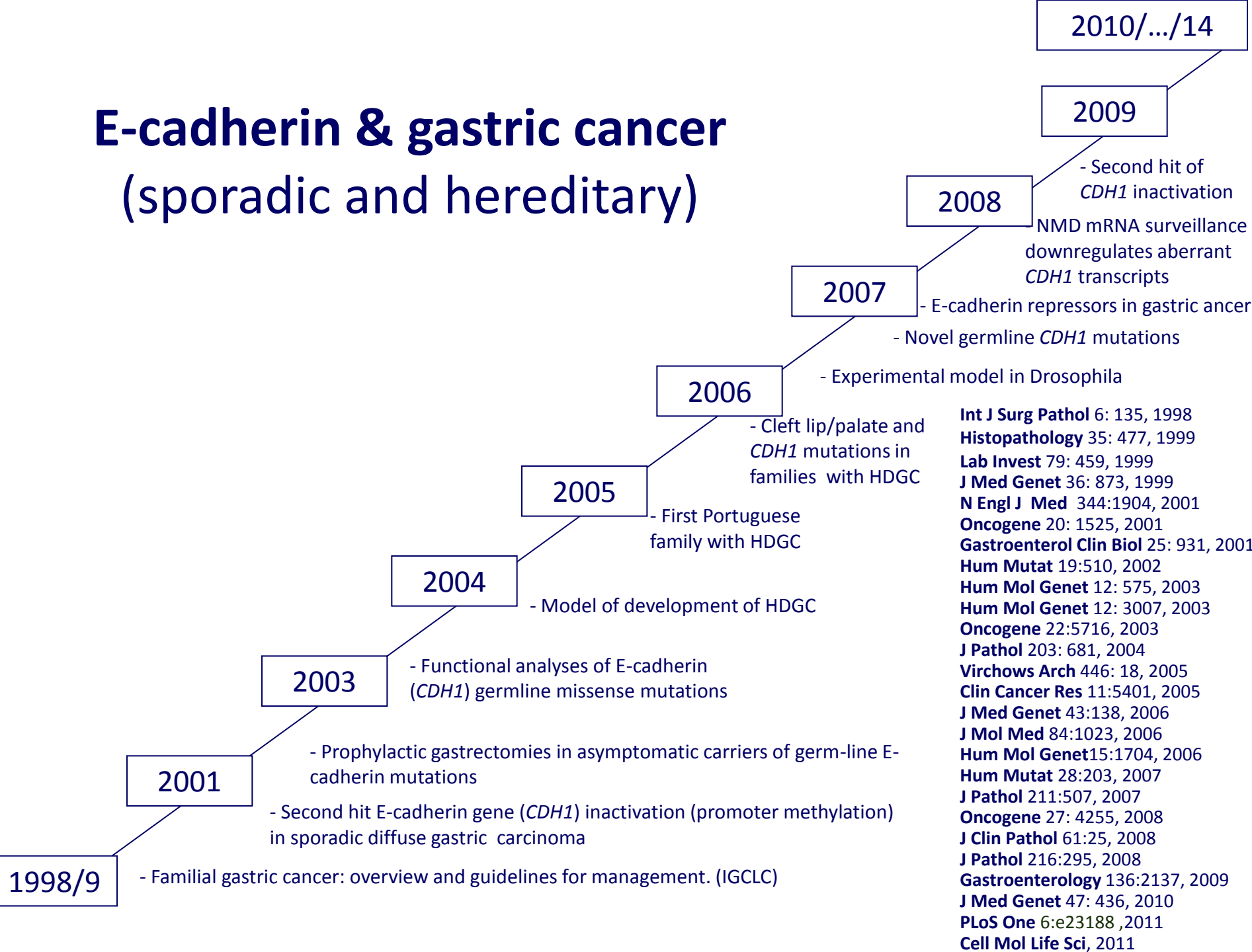
Hereditary Diffuse
Gastric Cancer (HDGC)



Guilford P *et al.* Nature 392:402,1998

*Gene map locus: [16q22.1](#) (MIM ID +192090)

E-cadherin & gastric cancer (sporadic and hereditary)

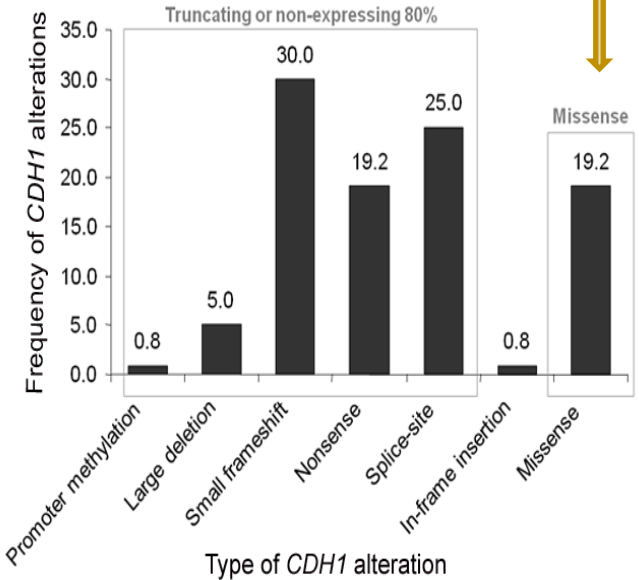
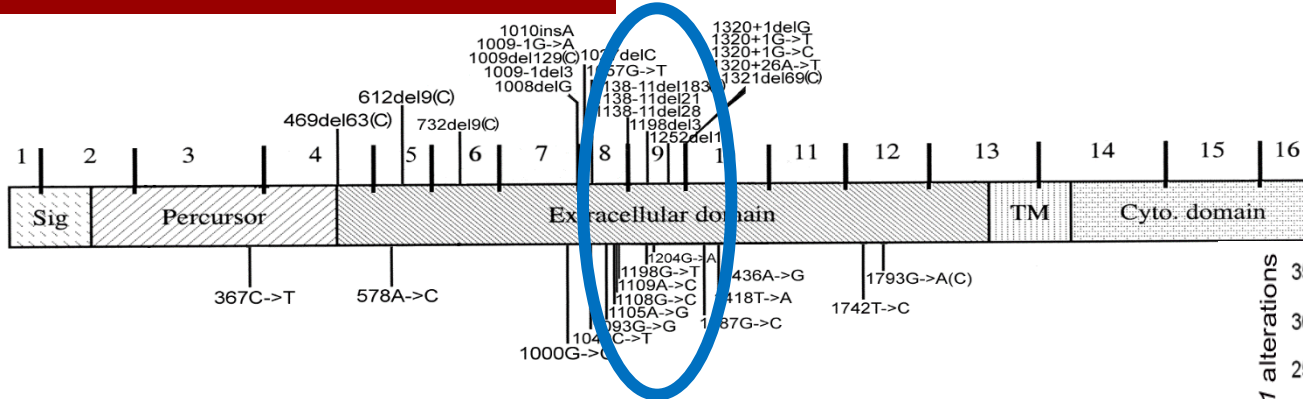


Hereditary Diffuse Gastric Cancer (HDGC)

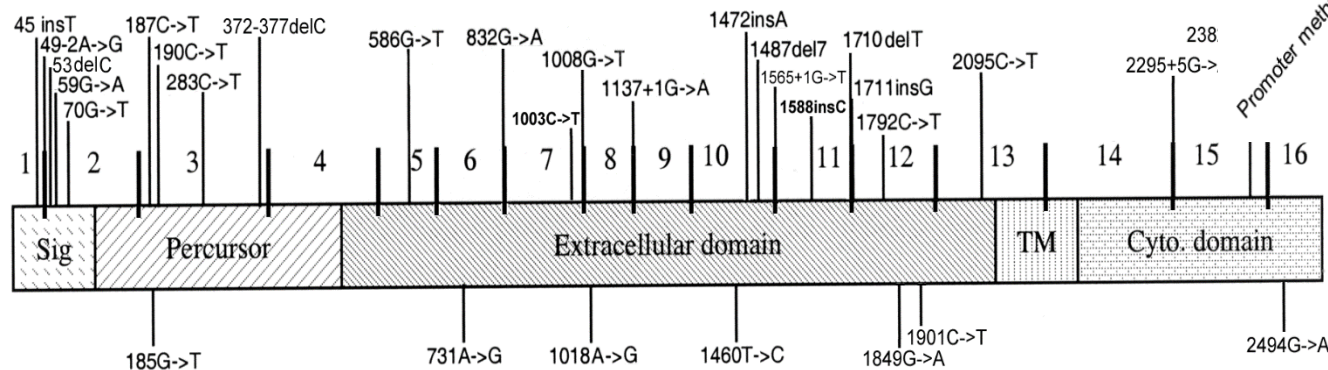
- Genetic susceptibility
(germline alterations)
- Molecular Pathology
(somatic alterations)
- Clinical features
- Histopathology

E-cadherin mutations in diffuse gastric cancer

SPORADIC - Somatic mutations



HEREDITARY - Germline mutations

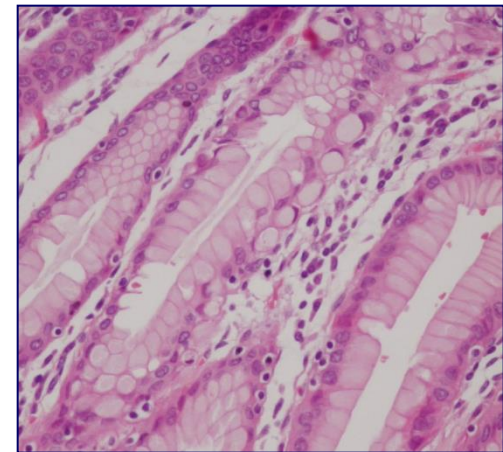
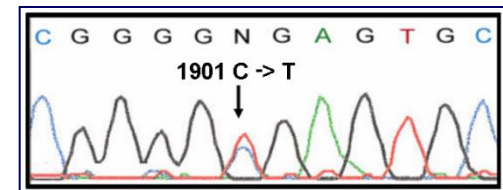
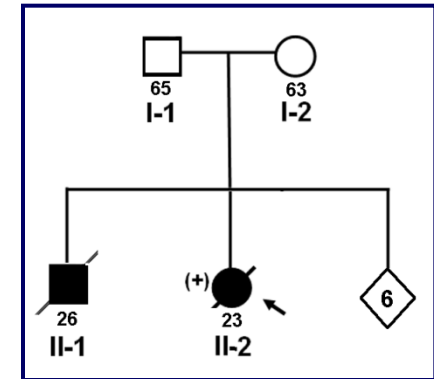


Validation of *CDH1* germline missense mutations

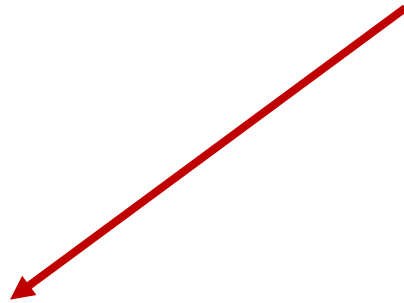
Table 2 E-cadherin germline missense mutations used for the statistical analysis

Variant	<1%	Co-segregation	Recurrence	SIFT ^a	Functional effect
Neutral (N) ^b	—	—	—	—	—
T118R	+	—	—	—	+
L214P	+	—	—	+	+
G239R	+	—	—	+	+
A298T	+	—	—	—	+
T340A	+	—	+	—	+
W409R	+	—	—	+	+
P429S	+	—	—	+	+
A592T	—	—	+	—	—
A617T	—	—	+	—	—
A634V	+	—	+	—	+
R732Q	+	—	—	+	+
P799R	+	—	—	+	+
V832M	+	+	—	+	+

Suriano G *et al.* J Mol Med 84:1023, 2006



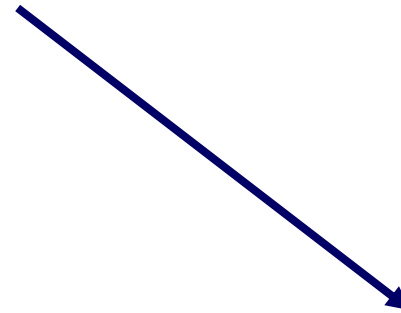
Missense mutations affect cell-cell adhesion, motility and invasion



T340A, A634V, W409R,
V832M, E757K

Functional Relevant

Adhesion, Motility,
Invasion



A617T,

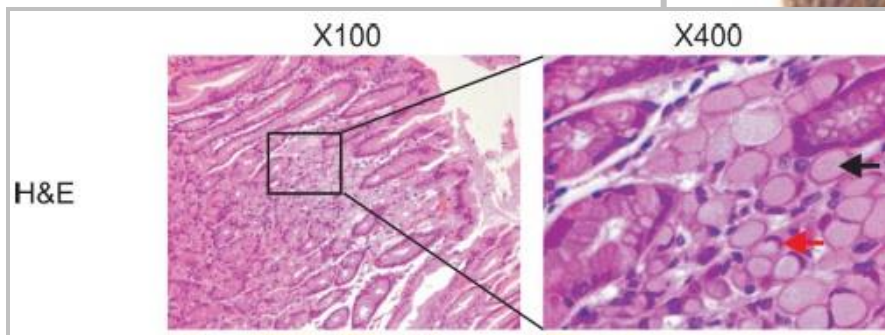
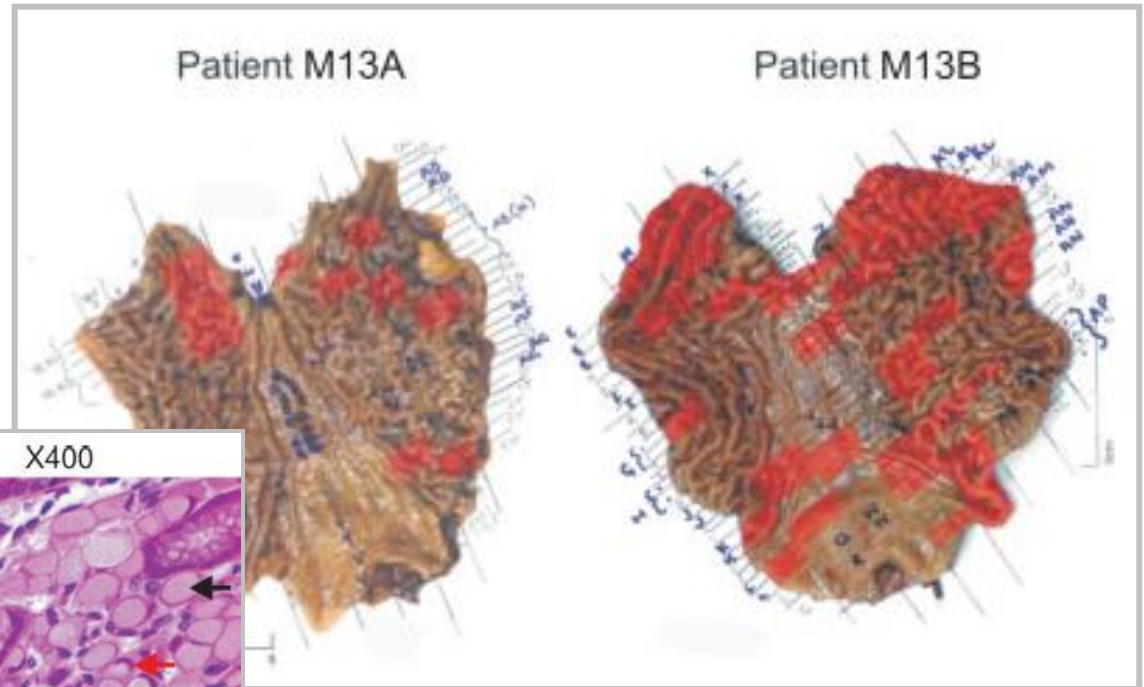
Functional Irrelevant

"neutral variants"

In vivo validation of *in vitro* assays of *CDH1* missense mutations

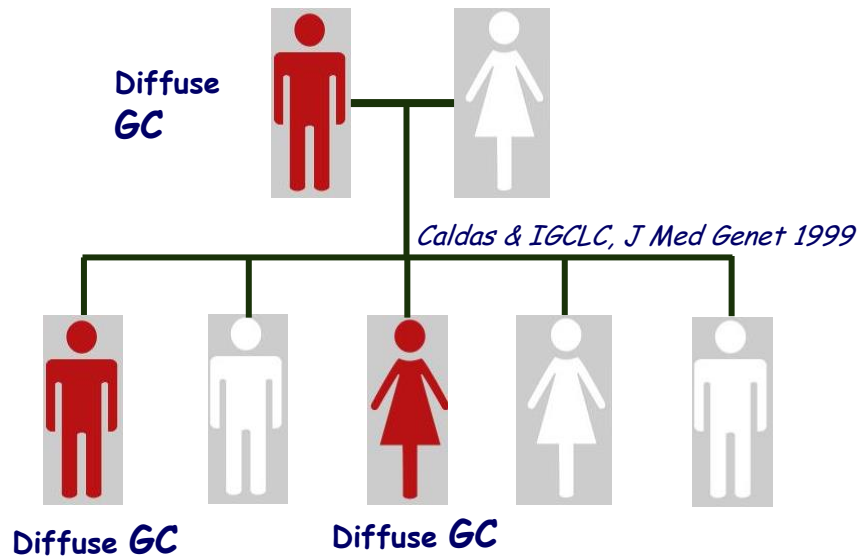
Table 2. Patients' characteristics and foci identified

Patient ID	Germline mutation	Mutation type	Age at surgery (years)	Sex	Length of time in surveillance programme	Number positive endoscopic biopsies/total taken (months prior to surgery)	Number of signet ring cancer foci identified in gastrectomy
M13A	64IT>C	Missense	23	F	6 Months	2/24 (2)	16
M13B			20	F	6 Months	6/24 (2)	66

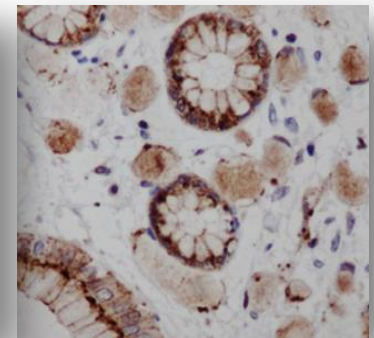
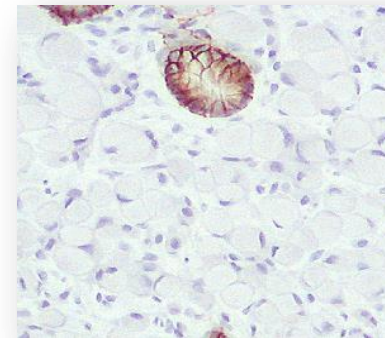
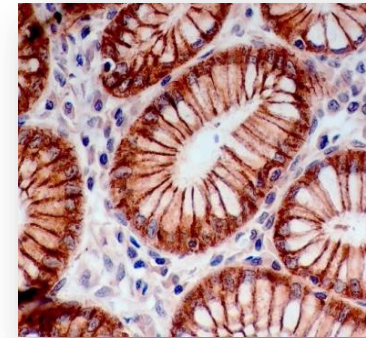


Late 2007

HDGC syndrome



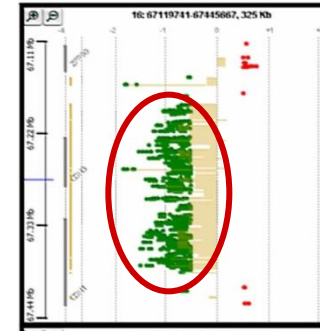
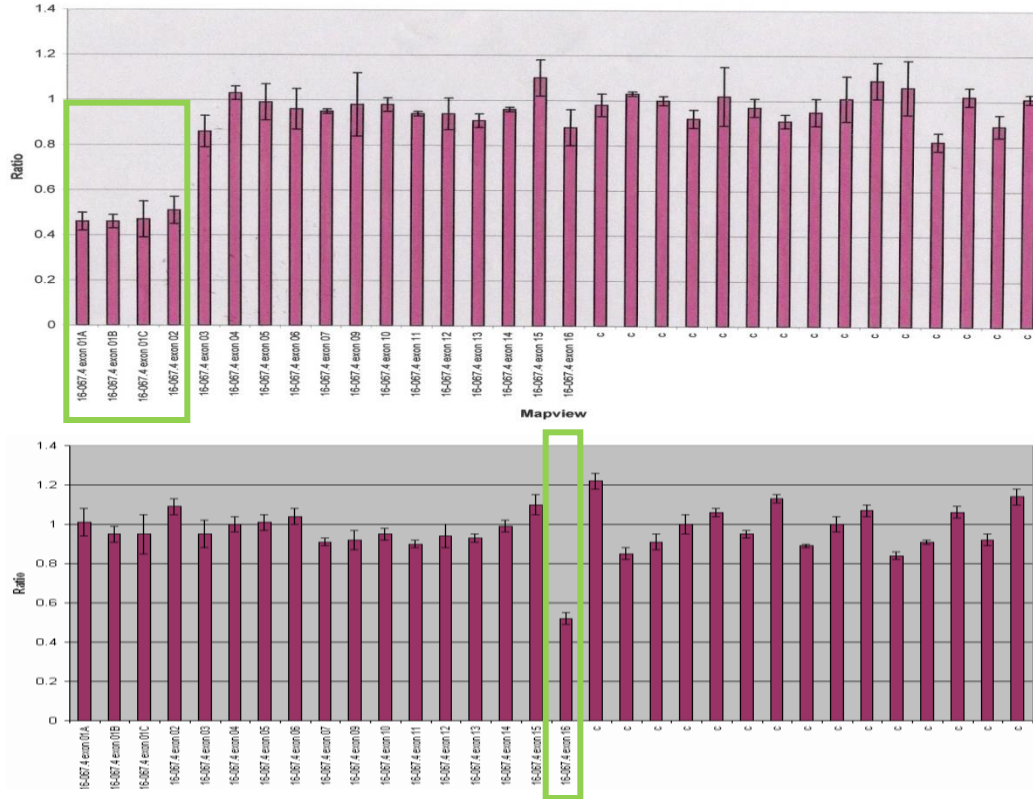
**30-40% *E-cadherin* gene (*CDH1*)
germline mutations**



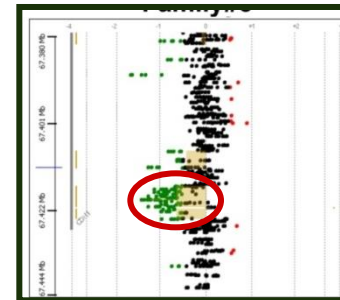
Guilford et al, Nature, 1998
Gayther et al, Cancer Res, 1999
Oliveira et al, Hum Mutat, 2002
Oliveira C et al, Exp Rev Mol Diagn, 2003
Oliveira et al, Eur J Cancer, 2004
Oliveira et al, Oncogene, 2004

Brooks-Wilson et al, J Med Genet, 2004
Oliveira C et al, Hered Cancer in Clin Pract, 2004
Oliveira C et al, Virchows Archiv, 2005
Suriano G et al, Clin Cancer Res, 2005
Oliveira C et al, Int J Surg Pathol, 2006
Kaurah P et al, JAMA, 2007

MLPA analysis and Array CGH



Deletions affecting the 5'-end of *CDH1*



Deletions affecting the 3'-end of *CDH1*

Large Alu associated **germline deletions of *CDH1*** in HDGC families: a new mechanism for disruption of E-Cadherin function

More recently...

An α -E-catenin (*CTNNA1*) mutation in hereditary diffuse gastric cancer

Ian J Majewski^{1,†}, Irma Kluijdt^{2,†},
Annemieke Cats³, Thomas S Scerri⁸,
Daphne de Jong⁴, Roelof JC Kluin⁵,
Samantha Hansford¹¹, Frans BL
Hogervorst², Astrid J Bosma¹, Ingrid
Hofland⁷, Marcel Winter⁷, David
Huntsman¹¹, Jos Jonkers⁶, Melanie
Bahlo^{8,9,10}, René Bernards^{1,*}

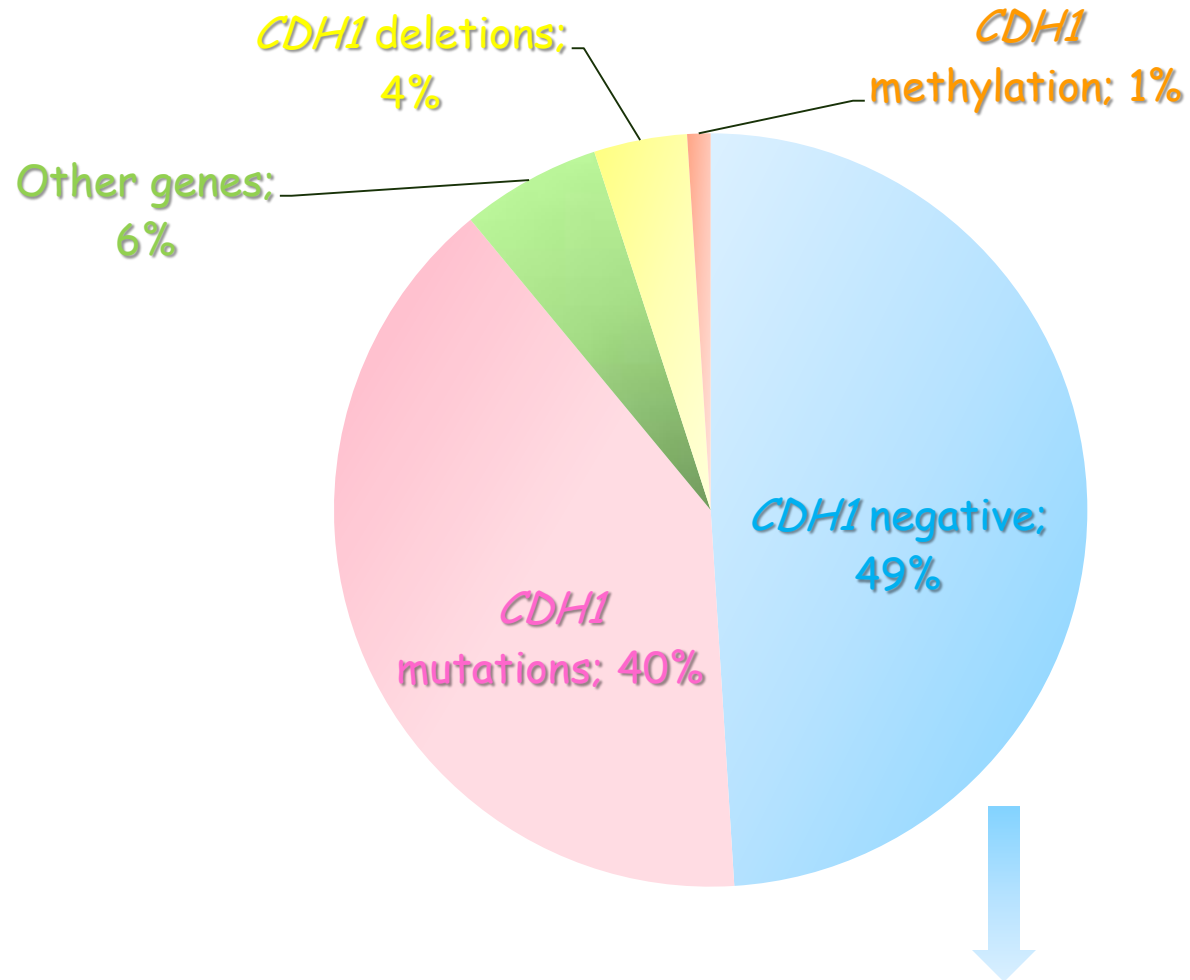
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Issue



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Volume 229, Issue 4, pages
621–629, March 2013

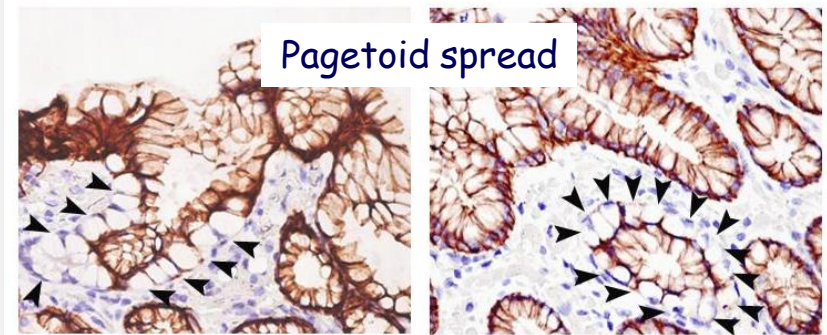
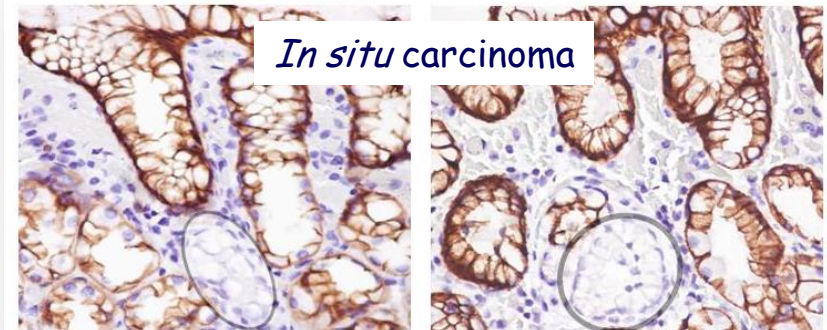
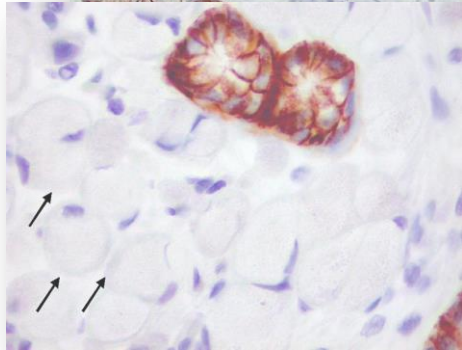
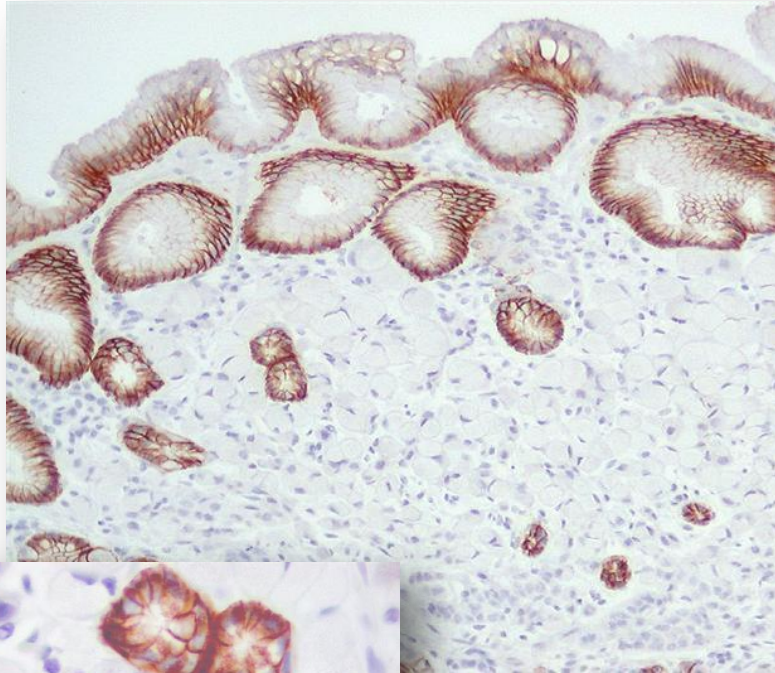


Currently, ongoing sequencing of the full 100kb
CDH1 locus in 90 HDGC patients

Molecular Pathology

(Somatic alterations)

Absent expression of E-cadherin (somatic inactivation of wild allele in the tumour)



CDH1 gene alterations in gastric carcinoma (Sporadic & Hereditary)

"1st HIT"

"2nd HIT"

Mutation

- Promoter methylation
- LOH
- "Second" mutation
- More than one

Grady et al. Nat Genet 26:16, 2000

Machado et al. Oncogene 20:1525, 2001

Oliveira et al. Gastroenterology 136:2137, 2009

Clinical features

Familial gastric cancer: overview and guidelines for management (International Gastric Cancer Linkage Consortium)



Caldas C, Carneiro F, Lynch H *et al*
Eur J Genet 36: 873, 1999

Clinical criteria for the identification of families with HDGC

Criteria for identification of HDGC families were defined by IGCLC in **1999**:

- 1) **Two** or more documented cases of diffuse gastric cancer in first/second degree relatives, with at least **one diagnosed before the age of 50**
- 2) **Three** or more cases of documented diffuse gastric cancer in first/second degree relatives, **independently of age**

Caldas C, Carneiro F, Lynch H *et al*: Familial gastric cancer: overview and guidelines for management. **J Med Genet** 36: 873, 1999

IGCLC criteria for genetic testing were updated in 2010:

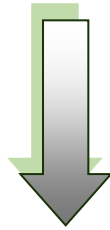
- 1) Idem
- 2) Idem
- 3) **Diffuse gastric cancer before the age of 40 years** without a family history
- 4) Families with diagnoses of **both diffuse gastric cancer and lobular breast cancer**, with one case before the age of 50 years

Fitzgerald R *et al*: Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. **J Med Genet** 47: 436-444, 2010

Familial gastric cancer: overview and guidelines for management

(International Gastric Cancer Linkage Consortium)

Carriers of germline E-cadherin
truncating mutations



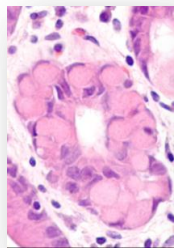
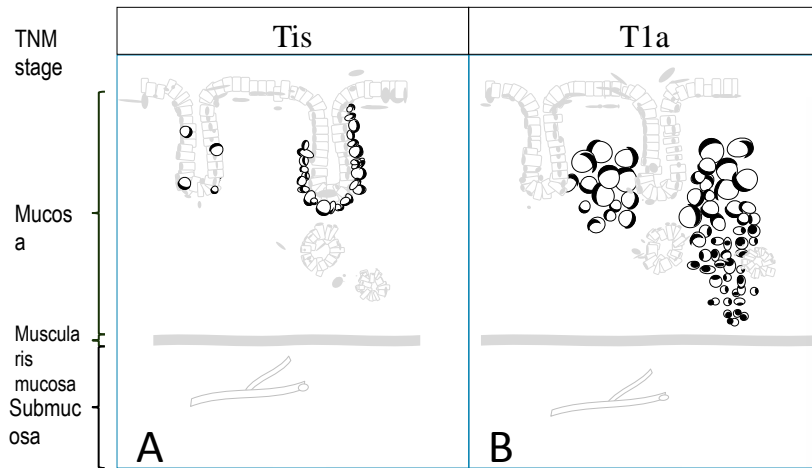
Intensive screening
Prophylactic gastrectomy

Caldas C, Carneiro F, Lynch H *et al*/
Eur J Genet 36: 873, 1999

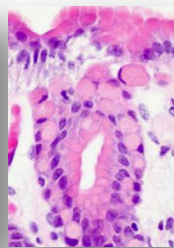
Histopathology

4-3 Hereditary Diffuse Gastric Cancer

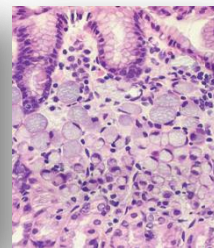
Fátima Carneiro
Amanda Charlton
David Huntsman



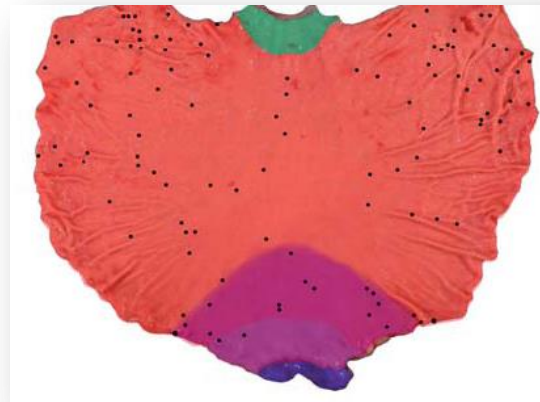
In situ
carcinoma



Pagetoid
spread

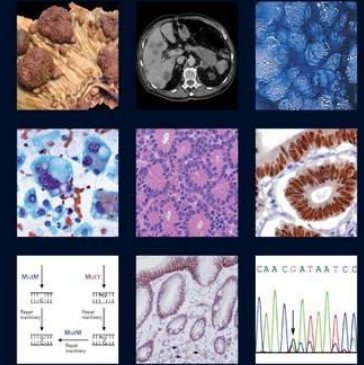


T1a intramucosal
signet-ring cell



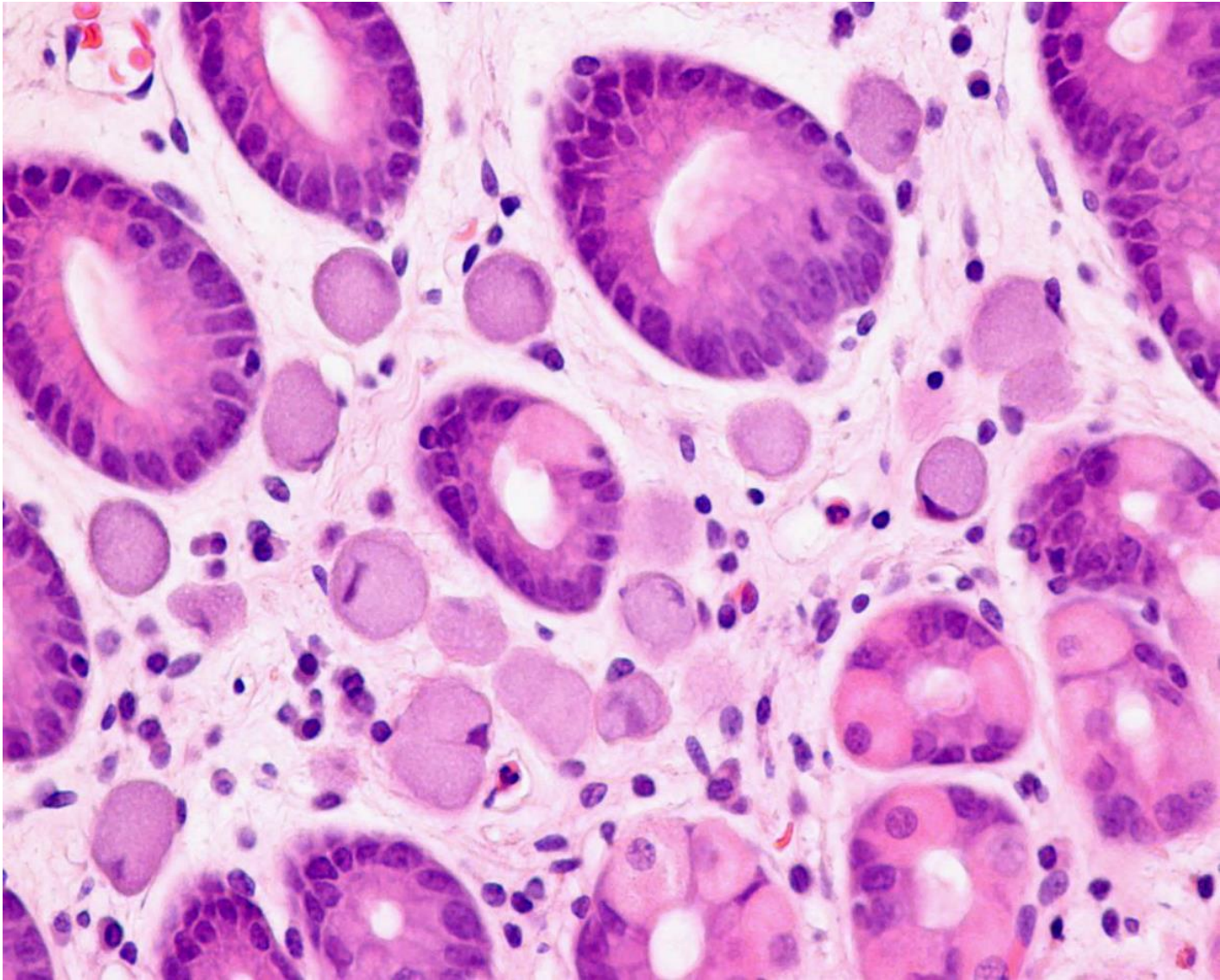
WHO Classification of Tumours of the Digestive System

Edited by Fred T. Bosman, Fátima Carneiro, Ralph H. Hruban, Neil D. Theise



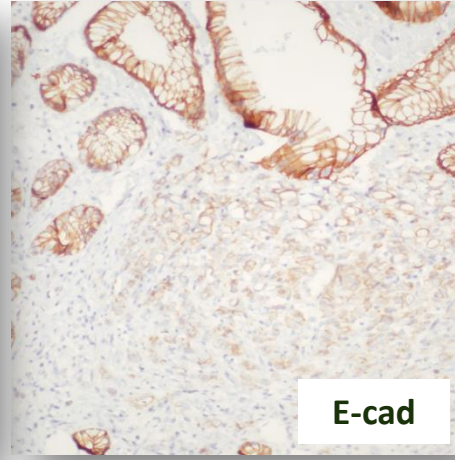
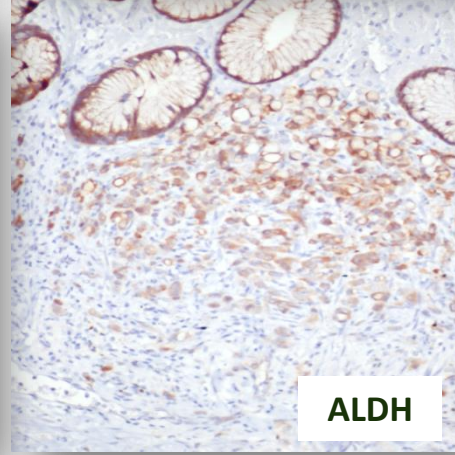
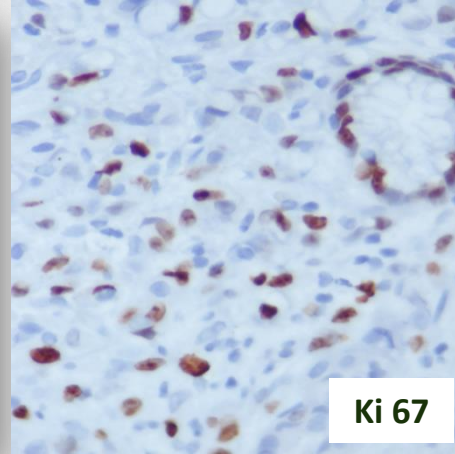
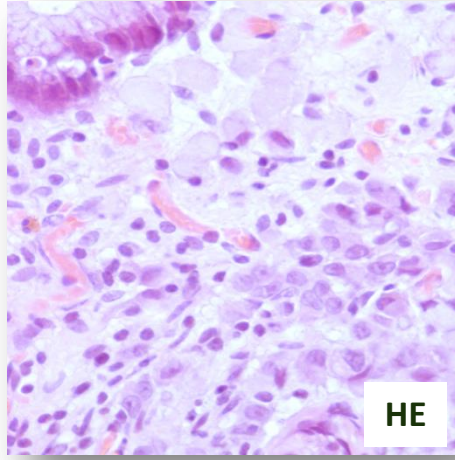
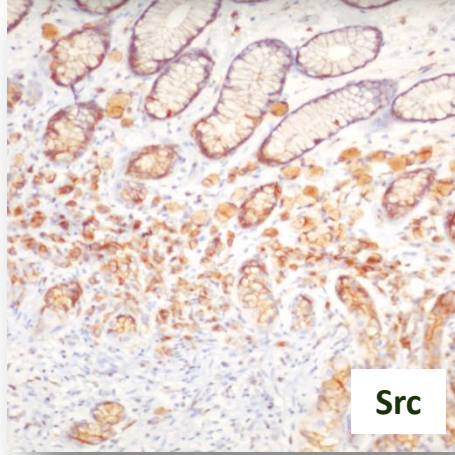
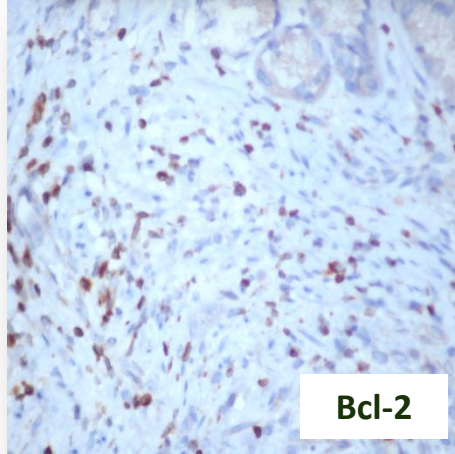
WHO

WHO - 4th Edition, 2010



Intramucosal signet-ring cell (diffuse) carcinoma

Intramucosal carcinoma



Aggressive pattern

Today's Science: Tomorrow's Medicine

European Journal of Human Genetics (2013) e1–e5; doi:10.1038/ejhg.2012.247

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www.nature.com/ejhg



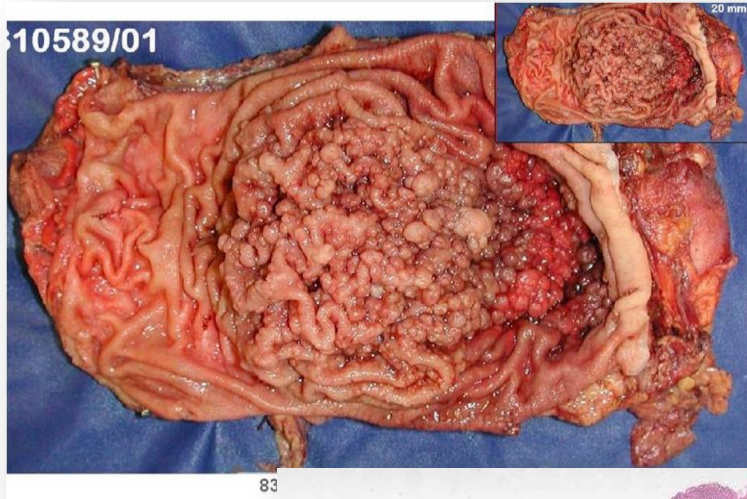
CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Hereditary diffuse gastric cancer (HDGC)

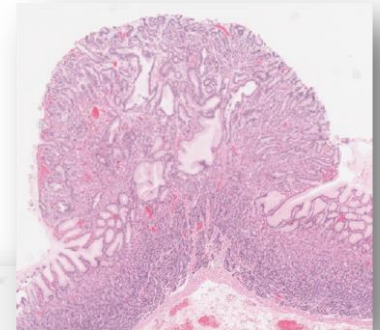
Carla Oliveira^{*,1,2}, Raquel Seruca^{2,3}, Nicoline Hoogerbrugge⁴, Marjolijn Ligtenberg^{4,5} and Fátima Carneiro^{2,3,6}

The brand new GAPPS syndrome...

(A new hereditary gastric cancer syndrome)

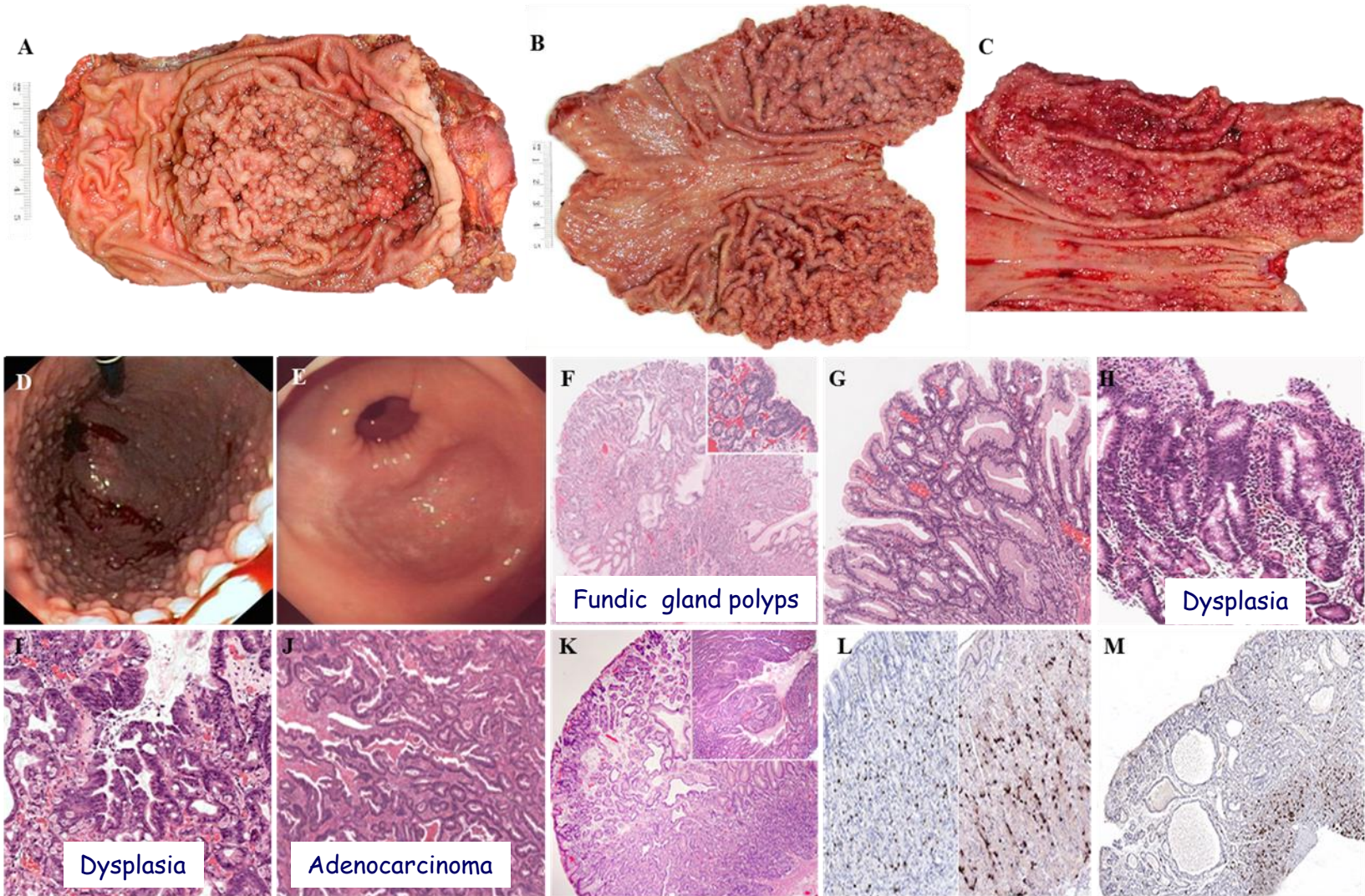


Proximal polyposis
of the stomach



Fundic gland polyps

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS): a new autosomal dominant syndrome.



Worthley et al; Gut 61:774-779, 2012

Genetic cause not known yet...

Hereditary gastric cancer

- Hereditary Diffuse Gastric Cancer - HDGC
(*CDH1* and *CTNNA1*)
- Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS) - HIGC
(Genetic defect not identified yet)

Take home lessons:

- Hereditary gastric cancer contributes to 1-3% of the burden of stomach cancer.
- Two syndromes have been identified:
HDGC
and
GAPPS

Take home lessons:

- HDGC is caused by germline alterations of the E-cadherin (*CDH1*) gene; prophylactic gastrectomy is recommended for asymptomatic carriers of pathogenic *CDH1* mutations.
- GAPPs syndrome is characterized by fundic gland polyposis, including areas of dysplasia or intestinal-type gastric adenocarcinoma. The genetic defect behind this syndrome has not yet been elucidated.



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José Carlos Machado
Céu Figueiredo
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Rita Mateus
Rachid Karam
Herculano Moreira
Manuel Cardoso de Oliveira
Fátima Carneiro
Raquel Seruca
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University of Cambridge UK

Paul Pharoah & Carlos Caldas



David Huntsman & David Owen



Parry Guilford, Vanessa Blair &
Amanda Charlton



Queensland Institute of
Medical Research

Georgia Chenevix-Trench



Thanks for your attention