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Results of Multi-Gene Panel Testing in a Gastric Cancer Cohort: It's Not All *CDH1*

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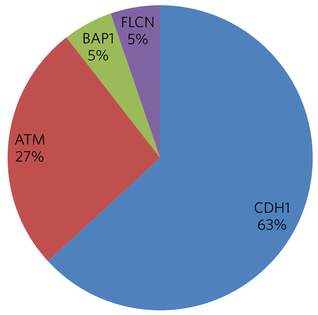
BACKGROUND

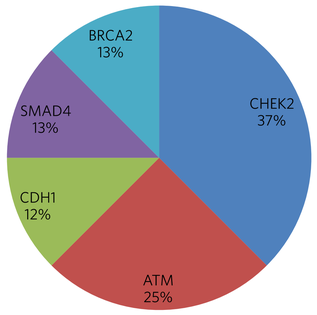
- Gastric cancer (GC) is the fifth most common cancer in the world and a genetic predisposition has been observed in some cases.
- Germline mutations in *CDH1* are known to be associated with hereditary diffuse gastric cancer (HDGC), and individuals with HDGC mostly present with diffuse, signet ring cell GC.
- Given that most diffuse GC present at later stages, genetic testing can help identify patients at risk so they can take measures to reduce their risk.
- Our study aimed to describe the results of multi-gene panel testing (MGPT) and the mutation spectrum observed among patients with a personal history of GC.

PATHOGENIC MUTATIONS: DIFFUSE vs. NON-DIFFUSE GASTRIC CANCER

Diffuse/signet-ring type (N=19)



Non-diffuse type (N=8)



METHODS

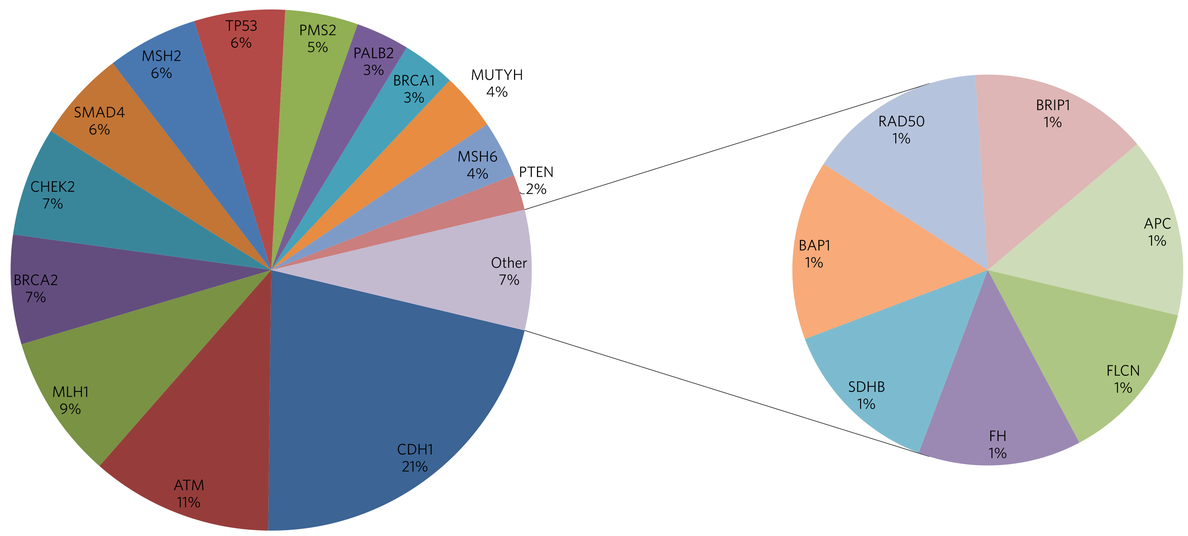
- MGPT results were retrospectively reviewed for all GC patients tested between June 2013 and June 2016 for five to 49 genes. Clinical history was obtained from test requisition forms.

RESULTS

- Of the 477 GC probands tested, 17.6% (n=84) were positive, 24.7% (n=118) were inconclusive, 57% (n=272) were negative and 0.6% (n=3) were *MUTYH* carriers.
- Of 205 with histology provided, 135 (65.9%) had diffuse-type/signet ring cell GC, 19 of which (9.2%) were positive, with most mutations in *CDH1* (n=12) and *ATM* (n=5).
- Of the 70 with non-diffuse GC, 8 (11.4%) were positive, with mutations in *CHEK2*, *ATM*, *CDH1*, *SMAD4*, and *BRCA2*.

PATHOGENIC MUTATIONS REPORTED FOR GASTRIC CANCER PROBANDS

- 89 germline mutations were detected across 21 genes in probands with GC
- *CDH1* mutations accounted for over 21% germline mutations (19/89), followed by *ATM* (11.2%), *MLH1* (8.9%), *BRCA2* (6.7%) and *CHEK2* (6.7%)
- Two individuals had mutations in two different genes (both with three primary cancers): the first had mutations in *MSH2* and *PTEN*, while the second had mutations in *ATM* and *BRCA1*.



OTHER PRIMARY CANCERS IN PROBANDS WITH MOST FREQUENT GENES

Gene	Other primary cancers (number of probands)
CDH1	breast (1), adenomatous polyps (1)
ATM	breast (2), prostate (2), esophageal (2), kidney (1), urothelial (1)
MLH1	colon (3)
BRCA2	breast (4), lymphoma (1)
CHEK2	breast (1), colon (1), small intestine (1)
SMAD4	adenomatous polyps (2), juvenile polyps (1)
MSH2	breast (1), colon (4), adenomatous polyps (2), uterine (1)
TP53	breast (1), colorectal (1), esophageal (1)
PMS2	none

PROBANDS WITH TWO PATHOGENIC MUTATIONS

Proband #1:

60 yo Caucasian female with a personal history of three primaries- colorectal cancer (dx. 43y), gastric cancer (dx. 52y) and colorectal cancer (dx. 56)
Family history of colorectal cancer on the maternal side
17-gene colon cancer panel was ordered which was positive for two mutations: *MSH2* c.1076G>C and *PTEN* c.1066A>G

Proband #2:

74 yo Caucasian male with a personal history of three primaries- kidney cancer (dx. 70y), prostate cancer (dx. 73y) and gastric cancer (dx. 74y)
Family history of colorectal cancer (father and son) and breast cancer (sisters)
32- gene comprehensive cancer panel was ordered which was positive for two mutations: *ATM* c.8494C>T and *BRCA1* EX11_IN11DUP

TAKE-HOME POINTS

- Overall, *CHD1* accounted for the largest proportion of mutations in GC probands (21%).
- For diffuse type GC, the largest proportion of mutations were found in *CDH1* (63%) whereas for the non-diffuse type, the largest percentage of mutations were in *CHEK2* (37%).
- Although hereditary GC is primarily thought to be associated with *CDH1*, we also identified mutations in genes known to cause increased risk for GC like *MLH1* as well as genes not known to cause increased risk for GC such as *ATM*.
- Further studies are needed to clarify whether other associations exist between GC histology and various germline mutations.

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