

E-cadherin germline mutations in Māori population

Alessandra Margherita De Scalzi¹, Bernardo Bonanni², Viviana Galimberti¹, Paolo Veronesi^{1,3}, Gabriella Pravettoni^{3,4} & Giovanni Corso^{*,1,3}

¹Division of Breast Surgery, European Institute of Oncology IRCCS, 20141 Milan, Italy

²Division of Cancer Prevention & Genetics, European Institute of Oncology IRCCS, 20141 Milan, Italy

³Faculty of Medicine, University of Milan, Italy

⁴Applied Research Division for Cognitive and Psychological Science, European Institute of Oncology, 20141 Milan, Italy

*Author for correspondence: Tel.: +39 0294375161; giovanni.corso@ieo.it

“The results of *CDH1* screening in the Māori are in marked contrast with findings from other GC patients.”

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CDH1 germline alterations are notoriously responsible for the development of hereditary diffuse gastric cancer (HDGC), an inherited autosomal cancer syndrome. Discovered for the first time in New Zealand in three Māori kindred, several *CDH1* alterations have also been identified in different ethnic populations to date. These mutations affect, with high frequency, areas with otherwise low incidence of gastric carcinoma (GC), as well as the Māori population. In this brief review, we report and describe the *CDH1* germline mutations recognized in this ethnicity.

GC incidence

GC is the fourth most common cancer worldwide, with about 934,000 new cases per year (8.6% of new cases of tumor per year) as estimated in 2002, after lung, breast and colorectal. GC is the second leading cause of cancer-related death, with 700,000 deaths annually. The incidence is significantly higher in less developed countries, with 42% represented by China alone. There is a wide variation in the distribution of GC between different areas of the world: high-risk areas include East Asia (China, Japan and Korea), Eastern Europe and parts of Central and South America. In Southern Asia, North and East Africa, North America, Australia, New Zealand and Africa the incidence rates are low (<10 per 100,000 in men) [1].

In Europe, GC is the fifth most common cancer, after colorectal, breast, lung and prostate, with an incidence of 149,000 new cases per year and a mortality rate of 116,000 per year. Eastern Europe is the area with the highest incidence of GC with 70,000 new cases per year just in the Belarus area [2].

The Māori ethnic group

The ancestors of the Māori were indigenous Polynesian people from Southeast Asia. They traveled by sea with typical canoes to New Zealand between 1250 and 1300 and for many centuries they lived in isolated communities. Thanks to this condition and due to New Zealand's distance from other landmasses, they developed peculiar culture, traditions, language and religion, distinguishing this tribal group from any other.

Nowadays the Māori ethnicity is a consistent part of New Zealand population; in 2010 it was estimated to be around the 15% (more or less 660,000 individuals) and the *te reo*, the Māori language, is one of the New Zealand's official languages since 1987, spoken by about 3.7% of the population.

A higher incidence of GC in Māori population was recognized in 1964 by Jones [3]. After examining this ethnic group for 30 years, it was observed that gastric cancer affected and led to death of over 25 family members. The first family tree under examination was composed of 98 members, 28 (28.6 %) of which developed a primary GC and two a colon cancer. Contrary to what might be expected, the incidence of different kind of cancers in this

family was average. Fourteen years-old was the earliest death reported in series, but the majority of deaths occurred before age of 40.

Among the 28 cases of gastric cancer, the distribution in gender was equivalent: 14 males and 14 females, with a mean age at diagnosis of respectively 36 and 31 years, showing a lower age of disease onset in females. The overall mean age at onset was 34 years. These data show a wide difference with general population in New Zealand, in which about the 80% of GCs occur in people over 60 years of age.

Data about the annual incidence of GC among New Zealand population are available online on the government website [4]. In this annual report, the population is split into Māori and non-Māori and it gives the opportunity to observe a significant increase in incidence in Māori of both sexes since 2000, in contrast with incidence rates in the non-Māori population which continued to uniformly decline [5].

E-cadherin germline mutations

A pathogenic CDH1 mutation is estimated to be present in about 40% of families with HDGC (defined as families from low-incident populations with two or more cases of gastric cancers with at least one proven DGC diagnosed in an individual before age 50) [6]. Oliveira *et al.* [7] indicated that germline CDH1 point or small frameshift mutations can be found in 30–50% of HDGC families.

The penetrance of HDGC is approximately 70% in CDH1 mutation carriers [6,8].

Women with a mutation in CDH1 and members of HDGC families have a lifetime risk of roughly 40% to develop a breast lobular carcinoma [9,10].

The CDH1 germline mutation is the *sine qua non* of getting the diagnosis of HDGC. In 2010, the International Gastric Cancer Linkage Consortium published updated recommendations [11] for genetic testing, surgery, endoscopy and pathology for HDGC with CDH1 mutations. Currently, genetic test criteria consider individuals diagnosed with DGC before the age of 40 years even if there is no family history. A test should also be performed in families with diagnoses of both DGC and lobular breast cancer, if at least one person has the onset before the age of 50 years. Testing is considered appropriate from the age of the consent. Before the genetic test, it is required to have an appropriate counseling and a discussion with the multidisciplinary team. A recognized CDH1 mutation in women increased the risk of developing a lobular breast cancer (LBC) and an annual mammography and breast MRI should be performed from the age of 35.

The CDH1 germline mutation carriers with a diagnosis of LBC have a high risk of HDGC syndrome [9]. *Vice versa*, an early onset of LBC might be the first presentation of HDGC.

Benusiglio *et al.* [12] identified CDH1 germline deleterious mutations in three bilateral LBC cases (age at onset <50 years) not fulfilling the International Gastric Cancer Linkage Consortium criteria.

These families have no history of HDGC in first- and second-degree relatives and no BRCA1 and BRCA2 mutations. In another series reported by Petridis, five CDH1 mutations have been identified in four bilateral early onset LBCs (age at onset <50 years) with no family history for HDGC [13]. Furthermore, Silva *et al.* reported two female patients with LBC (ages 60 and 51), both carriers of germline CDH1 mutations, who underwent prophylactic gastrectomy that revealed foci of intramucosal DGC in both cases [14].

Very recently, two potentially pathogenic CDH1 alterations were reported in patients with LBC without a family history of gastric tumor [15,16]. Considering only individuals with LBC and excluding genealogical chart with gastric tumor occurrence, a total of 495 female LBCs from six independent original studies were screened for CDH1 genetic alterations. Sixteen (3.2%) novel CDH1 germline variants have been identified. Bilateral LBC was diagnosed in 14.3% of cases (6/63), positive family history for BC was reported in 40.3% and the mean age at onset was about 45 years-old [17].

DGC lesions are submucosal and the screening with endoscopy with multiple biopsies are inadequate for early diagnosis [18]. A possible diagnostic delay and the high mortality rate made the prophylactic total gastrectomy a viable option for mutation carriers [8,19,20]. The prophylactic surgery should be strongly evaluated in centers of excellence. As every prophylactic surgery, also the choice of a total gastrectomy may be an extremely problematic emotional experience [20–22] and a compassionate genetic counseling should be guaranteed.

For the CDH1 pathogenic mutation carriers that refuse the option of a prophylactic surgery, a strictly endoscopic surveillance at centers of expertise is highly recommended. In the same way also all the patients who have genetical modification of undetermined significance and all the members of families in which a germline mutation has not yet been identified should be controlled every year [23].

E-cadherin genetic screening in Māori population

In 1998, Guilford *et al.* first detected three different germline mutations in *CDH1* gene in three Māori families from New Zealand. In those families with a high incidence of DGC were found a splice site (100BG>T), a frameshift (238 2- 238 6, Cins) and a premature termination (TAG, 2095C>T) germline mutation in the E cadherin gene [24], respectively.

In 1999, the International Gastric Cancer Linkage Consortium defined this predisposition as HDGC [25]. Other international studies subsequently identified novel *CDH1* germline alterations in families Māori-unrelated. Notably, the majority of these pathogenic *CDH1* germline alterations ‘affect’ some countries otherwise classified as low risk for GC, as well as New Zealand, with higher frequency [26]. Thus, environmental factors, such as food consumption and lifestyle habits, have been investigated in association to stomach carcinogenesis and tumor development in countries with high incidence of GC [27].

In a recent study by Hakkaart *et al.* [28], 17 *CDH1* germline alterations were identified in 94 Māori individuals with GC (18%), with 34% of them diagnosed with HDGC, one of the highest frequencies ever reported in literature.

In details, five pathogenic alterations (three nonsense, one frameshift and one missense) were identified. The three nonsense mutations (190C>T, 1792C>T and 2287G>T) and one frameshift mutation (2381_2386insC) were identified in four cases each, while the deleterious missense mutation (2195G>A) was identified in a single case.

The nonsense and frameshift mutations had already been identified previously in Māori families in New Zealand [29]. 2195G>A is a splice siting alteration that creates a new acceptor splice site and a large deletion in the E-cadherin protein, identified in a family from the UK with HDGC diagnosis [30]. 2195G>A had previously been detected in two families of northern European origin with HDGC [31]. Finally, 2195G>A was reported for the first time in New Zealand Māori population.

Conclusion

The results of *CDH1* screening in the Māori are in marked contrast with findings from other GC patients. In fact, incidence of *CDH1* germline mutations is higher in the Māori in comparison with other ethnicities. New Zealand is considered a low-risk GC area and frequency of E-cadherin germline alterations is rather high, while in high risk GC areas *CDH1* germline mutations are rarely identified. It is reasonable to imply that *CDH1* pathogenic germline alterations are strong contributors to the high frequency of HDGC in countries with low incidence of gastric carcinoma, as well in Māori population.

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