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Familial gastric cancer – aetiology and pathogenesis

Miriam Barber BSc (Hons)
MRC PhD Student

Rebecca C. Fitzgerald* MACantab, MD, MRCP
MRC Group Leader and Honorary Consultant Gastroenterologist
MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Hills Road, Cambridge CB2 2XZ, UK

Carlos Caldas MD, FACP, FRCP, FMedSci
Professor of Cancer Medicine
Cancer Genomics Program, Department of Oncology, University of Cambridge, Hutchison/MRC Research Centre, Hills Road, Cambridge CB2 2XZ, UK

Gastric cancer is the second most common cause of cancer death worldwide. It is estimated that 5–10% of gastric cancer cases have a familial association; however, knowledge concerning the genetic predisposition to familial gastric cancer is currently limited. In this chapter we discuss what is known about the aetiology and pathogenesis of both the diffuse and intestinal forms of familial gastric cancer. We focus particularly on hereditary diffuse gastric cancer because the discovery of germ-line E-cadherin mutations in a number of affected families has opened the prospect of identifying gene carriers, with implications for clinical management. The interplay of other conventional risk factors, such as *Helicobacter pylori* infection, with genetic factors is also discussed. It is hoped that understanding the genetic basis for familial gastric cancer will facilitate the development of clinically useful screening and preventative procedures.

Key words: International Gastric Cancer Linkage Consortium; hereditary diffuse gastric cancer; E-cadherin; intestinal familial gastric cancer; *Helicobacter pylori*; Epstein–Barr virus.

Gastric cancer has been known to have a familial association for approximately 200 years, and it is clearly documented in Napoleon Bonaparte's kindred.[1] Not only did Napoleon himself succumb to gastric cancer but several other members of his family – including his father, grandfather, brother and three sisters – are all reported to have

* Corresponding author. Tel.: +44 1223 763 292; Fax: +44 1223 763296.
E-mail address: ref29@hutchinson-mrc.cam.ac.uk (R.C. Fitzgerald).

died of stomach cancer, many at a young age (although autopsies were not carried out in most cases).[1] Studies suggest that there is a strong familial component in about 5–10% of gastric cancer cases, and although this is only a small percentage the implications are profound for the affected families. The familial aggregation is more common in the diffuse than in the intestinal phenotype, such that the increased risk for relatives of patients with diffuse-type gastric cancer is 7.0-fold compared to a 1.4-fold increased risk for relatives of patients with intestinal-type cancer.[2] Understanding the causative genes for hereditary forms of cancer provides an opportunity to screen the family members who are at risk and offers preventative treatment. Furthermore, it is hoped that knowledge of the molecular genetics of familial cases may also provide insight into mechanisms of carcinogenesis that are relevant for sporadic cases.

HEREDITARY DIFFUSE GASTRIC CANCER

In 1999 Guilford et al coined the term hereditary diffuse gastric cancer (HDGC) to group together patients who have an autosomal dominant inheritance pattern for a diffuse-type gastric cancer syndrome.[3] In the same year the inaugural meeting of the International Gastric Cancer Linkage Consortium (IGCLC) was held to determine the diagnostic criteria and to provide recommendations for the clinical management of affected patients and their families.[4] It was hoped that the criteria established by the IGCLC would help to recruit HDGC patients with complete pedigrees and to encourage clinicians to provide suitable specimens for research. Accumulation of such families will help to ascertain data on the worldwide prevalence, environmental risk factors, tumour spectrum, natural history, possible genotype/phenotype associations, the efficacy of prospective clinical surveillance and the predisposing genes associated with HDGC.[4]

The criteria currently used by the IGCLC to define HGDC are:[4]

1. Any family with two documented cases of diffuse gastric cancer in first- or second-degree relatives, with one case under the age of 50; and
2. Three or more documented cases of diffuse gastric cancer in first- or second-degree relatives at any age.

These criteria were set to be over-inclusive in order to uncover novel predisposing genes. In 2004 it was documented that there were at least 80 families fulfilling the IGCLC criteria for HDGC.[5]

In 2004 Brooks-Wilson et al expanded the criteria to include additional cancer phenotypes that may be associated with HDGC. These modified criteria are:[6]

1. Any family with two documented cases of diffuse gastric cancer in first- or second-degree relatives, with one case under the age of 50;
2. Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer;
3. Any individual diagnosed with diffuse gastric cancer before the age of 45;
4. Any individual diagnosed with both diffuse gastric cancer and lobular breast cancer;
5. One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer;
6. One family member diagnosed with diffuse gastric cancer and another with signet-ring colon cancer.