Identity

Alias: Signet ring carcinoma or isolated cell type carcinoma.

Inheritance: Autosomal dominant with high penetrance (about 80%), average age of onset is in the 4th decade of life but it could be as early as the teens to the seventies. Germline mutations in CDH1 gene have been associated with this condition (Gayther et al., 1998; Guilford et al., 1998).

Clinics

Note

Criteria for diagnosis (Brooks-Wilson et al., 2004):
- Two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years.
- Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer.
- An individual diagnosed with diffuse gastric cancer before 45 years of age.
- An individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria met).
- One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other criteria met).
- One family member diagnosed with diffuse gastric cancer and another with signet ring colon cancer (no other criteria met).

Phenotype and clinics

HDGC forms less than 3% of all gastric cancers (Stone et al., 1999). It often affects younger people in contrast to the other types of gastric cancer. It consists of scattered clusters of poorly differentiated cells involving a large area of the stomach without a macroscopically recognisable margin or formation of a mass or ulcer (linitis plastica).

There is no known association between genotypic and phenotypic character of the disease (Kaurah and Huntsman, 2006).

Malignant risk: Four fifths of female carriers with CDH1 gene mutations are estimated to develop HDGC by age of 80 years with an additional 40% risk for lobular breast cancer, adding up to 90% for both cancers, while two thirds of males are expected to develop gastric cancer by the same age (Paul et al., 2001).

Treatment

Aim of the management is: (1) Curative treatment through early detection and resection of the tumour completely, but unfortunately gastric cancer especially HDGC are usually incurable at presentation. (2) Identifying Germline mutation in CDH1 can provide help and support for family members who are unaffected but carrier of the genetic mutations by developing a plan to reduce the risk of cancer (Brooks-Wilson et al., 2004), through either (a) prophylactic gastrectomy which may be life saving as cancer cells have been detected in all resected stomach specimens in asymptomatic carriers (Huntsman et al., 2001), but with high morbidity and mortality (22-30% and 4-5% respectively (Kelsen et al., 2008)), or through (b) extensive biannual chromoendoscopic surveillance which has its limitation in detecting submucosal lesions in a normal looking mucosa, therefore the best preventive approach is yet to be established (Cisco et al., 2008).

In view of increase risk of colorectal cancer by 2-3 times and lobular breast cancer in females, surveillance colonoscopy every 3-5 years and regular MRI check of
the breast may be required (Cisco et al., 2008; Porter et al., 2002).

**Prognosis**

Overall survival in gastric cancer is poor with 28% at 5 years and 20% at 10 years. However if the cancer is detected at early stages (i.e. confined to mucosa and submucosa), >90% will be alive at 5 years compare to 10-20% in advanced gastric cancer even when potentially curative surgery has been carried out (Kelsen et al., 2008; Leung et al., 2009).

**Genes involved and proteins**

**CDH1**

**Location**

16q22.1

**DNA/RNA**

Description: The gene consists of 16 exons and a 65-kb-long intron 2 that span around 100 kb (Berx et al., 1995).

**Protein**

Description: E cadherin is a transmembrane calcium dependant glycoprotein (728 AA) with cytoplasmic domain which binds to actin cytoskeleton via catenins (catenin alpha, catenin beta and catenin gamma), single transmembrane domain, and extracellular domains which adhere to neighbouring cells and form a tight homophilic bond which is an important part in cell-cell adhesions, tissue architecture, cell differentiations and proliferations (Conacci-Sorrell et al., 2002; Roy and Berx, 2008).

Function: CDH1 gene encodes for Cadherin protein which plays an important role in maintaining normal cell physiology like differentiation, growth, motility and tissue architecture through tight cell-cell adhesions (Conacci-Sorrell et al., 2002; Robertson and Jankowski, 2008).

Loss of cell adhesions have been noted in cancers for a long time. CDH1 suppression has been associated with poorly differentiated, aggressive, metastatic cancers. Mutation in E-cadherin is also associated with breast, colorectal cancers, thyroid, endometrial, ovarian, head and neck, skin, prostate, bladder cancer and other tumours (Birchmeier, 1995).

**Mutations**

Germinal: Germline mutations in CDH1 have been associated with HDGC. First mutations were described by Guilford et al. in three Maori families in New Zealand in 1998 (Guilford et al., 1998). Nowadays more than 50 different types of mutations have been described and new ones are emerging (Robertson and Jankowski, 2008). Types of mutations described are mainly truncating and missense mutations.

Up to 50% of families meeting the criteria above, which was set by the International Gastric cancer Linkage Consortium (IGCLC) in 2004, will have mutations in CDH1 (Brooks-Wilson et al., 2004). Promoter methylation of the wild type allele in the mutated CDH1 is associated with loss of gene expression and might work as a "second genetic hit" predisposing to cancer and explain the absence of loss of heterozygosity in this condition (Grady et al., 2000).

**References**


This article should be referenced as such: