Genetics/Genomics/Proteomics of Gastric Adenocarcinoma

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KEYWORDS

• Gastric cancer • Molecular genetics • Hereditary gastric cancer • Genomics
• Proteomics

KEY POINTS

- Hereditary diffuse gastric cancer can be caused by epithelial cadherin mutations for which genetic testing is available.
- Inherited cancer predisposition syndromes can be associated with gastric cancer.
- Chromosomal and microsatellite instability occur in gastric cancers.
- Several consistent genetic and molecular alterations have been identified in gastric cancers.
- Biomarkers and molecular profiles are being discovered with potential for diagnostic, prognostic, and treatment guidance implications.

INTRODUCTION

Gastric adenocarcinomas comprise the vast majority of malignant tumors arising from the stomach. Although other histopathologic forms of stomach tumors exist, they are rare in occurrence. Gastric cancer (GC) remains a significant worldwide health burden. GCs exhibit heterogeneity in clinical, biologic, and genetic aspects. The complexity of the genetics involved in gastric adenocarcinoma is reflected in the temporal, regional, and gender variation in GC incidence rates. A better understanding of these phenomena through molecular and genetic studies of gastric tumor genesis is anticipated to provide important insights into cancer development in general and lead to earlier diagnosis and better management options.

INHERITED SUSCEPTIBILITY

Familial Clustering

Most cases of GC appear to occur sporadically, without an obvious hereditary component. Familial clustering has been observed in approximately 12% of gastric carcinoma

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cases, with a dominant inheritance pattern.[1] Notably, Napoleon Bonaparte apparently suffered from GC involving most of his stomach and may have had other family members (ie, his father and sister) afflicted as well.[2,3] In the Swedish Family Cancer Database, when a parent presented with gastric carcinoma, offspring showed an increased risk of the concordant carcinoma, with a Standardized Incidence Ratio (SIR) of 1.59, only at ages older than 50 years.[4] The increased risk from sibling GC probands (SIR of 5.75) was noted for those diagnosed before age 50 years. Taken together, these findings suggest that some of the familial risk factors are likely to be environmental, siblings being at a higher risk than offspring-parent pairs, consistent with the transmission patterns of *Helicobacter pylori* infection.

Case-control studies have observed consistent (up to threefold) increases in risk for GC among relatives of patients with GC.[5] A population-based control study found an increased risk of developing GC among first-degree relatives of affected patients (odds ratio [OR] = 1.7 with an affected parent, OR = 2.6 with an affected sibling), with the risk increasing (OR up to 8.5) if more than one first-degree relative was affected.[6] Interestingly, a higher risk was noted in individuals with an affected mother versus an affected father. Studies have shown a slight trend toward increased concordance of GCs in monozygotic twins compared with dizygotic twins.[7] A genomic analysis of 170 affected sib-pairs from 142 Japanese families with GC yielded several chromosomal regions, with the strongest linkage at 2q33-35, harboring potential susceptibility genes.[8]

Inherited Predisposition Syndromes

Inherited predisposition cancer syndromes are thought to comprise only 1% to 3% of all GCs.[9] Several genetic susceptibility traits with an inherited predisposition to GC development exist. Some are well-characterized clinically with their underlying genetic alterations being unveiled and are described in this article.

Hereditary diffuse gastric cancer

Three large Maori families with an obvious autosomal dominant, highly penetrant inherited predisposition to the development of GC, having sufficient power with which to perform productive linkage studies, revealed linkage to the epithelial cadherin (*E-cadherin*)/*CDH1* locus on 16q22.1 in 1998.[10] Further analysis of these families demonstrated association of GC development with germline mutations in the *E-cadherin* (*CDH1*) gene. Since then, multiple germline *E-cadherin* mutations have been reported in more than 100 families throughout the world.[11] The CDH1 gene mutations have been scattered across the 16 exons this gene encompasses, with approximately 70% being truncating and 30% missense in nature.[12,13] Moreover, there have even been large deletions of the E-cadherin gene identified in a small percentage (4%) of hereditary diffuse gastric cancer (HDGC) families, likely involving nonallelic homologous recombination in Alu repeat regions.[14]

The first definition of the hereditary diffuse GC trait, which is the only inherited cancer syndrome dominated by GC, was made in 1999.[15] The ages of onset for diffuse GC in subjects harboring germline *E-cadherin* mutations ranged from 14 to older than 70 years. The cumulative risk estimate for advanced GC by 80 years of age was estimated to be 67% for men and 83% in women with wide confidence intervals, as these were based on 11 HDGC families.[16] The mean age at GC diagnosis was 40 years in this study. Additionally, female *CDH1* mutation carriers had a high risk of developing lobular breast cancers with a lifetime risk of 60% by the age of 80 years. The incomplete penetrance of germline *E-cadherin* mutations was seen in several obligate carriers, who remained unaffected even in their eighth and ninth decades of life. Variable penetrance is suggested in the larger HDGC families and a later onset of the