Genetic mutations identified for type of gastric cancer

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Researchers have identified novel genetic mutations that are linked to hereditary diffuse gastric cancer, with these mutations being due to both independent mutational events and common ancestry, according to a study in the June 6 issue of JAMA. This study is being released early to coincide with its presentation at the annual meeting of the American Society of Clinical Oncology.

According to background information in the article, gastric cancer is the second most common cause of cancer death worldwide. There are two major variants of this cancer: an intestinal type and a diffuse type. "A decline in the overall incidence of gastric cancer can be attributed primarily to a decrease of the intestinal variant of gastric cancer with the diffuse type remaining stable or possibly even increasing." Hereditary diffuse gastric cancer (HDGC) is caused by mutations in the gene CDH1, and is characterized by an increased risk for diffuse gastric cancer and lobular breast cancer. "The identification of CDH1 mutations offers the opportunity of cancer risk-reduction strategies for unaffected at-risk individuals," the authors write.

Pardeep Kaurah, M.Sc., of the BC Cancer Agency, Vancouver, and colleagues conducted a study to assess the frequency of mutations in the CDH1 gene and whether these mutations occurred due to independent mutational events or common ancestry. The study included 38 families diagnosed clinically with HDGC, who were analyzed for CDH1 mutations. Twenty-six families had at least two gastric cancer cases with one case of diffuse gastric cancer in a person younger than 50 years; 12

families had either a single case of diffuse gastric cancer diagnosed in a person younger than 35 years or multiple cases of diffuse gastric cancer diagnosed in persons older than 50 years.

Thirteen mutations (6 novel) were identified in 15 of the 38 families (40 percent detection rate). Two families from this study plus two additional families carrying the novel 2398delC mutation shared a common haplotype (a group of alleles of different genes on a single chromosome that are closely enough linked to be inherited usually as a unit), suggesting a founder effect (a population group with an unusual frequency of a gene due to there having been only a small number of original members, one or more of whom had that gene). All four families originate from the southeast coast of Newfoundland.

Due to concentrations of lobular breast cancer cases, two branches of this family had been diagnosed as having hereditary breast cancer and were tested for BRCA mutations. Within these four families, the cumulative risk by age 75 years in mutation carriers for clinically detected gastric cancer was 40 percent for males and 63 percent for females and the risk for breast cancer in female mutation carriers was 52 percent.

"Our results confirm that between 30 percent and 40 percent of families with a positive family history of gastric cancer and more than 50 percent of families with 2 diffuse gastric cancer cases diagnosed prior to age 50 years will carry germline mutations in the CDH1 gene," the researchers write.

"This extended family with the 2398delC founder mutation is a useful resource for determining risk-modifying factors in the development of diffuse gastric cancer or lobular breast cancer, such as diet or genetic polymorphisms, and for studying secondary genetic events that lead to cancer formation. The identification of this mutation could permit

population-based screening of diffuse gastric cancer within specific regions of Newfoundland. Testing for the founder mutation will be particularly valuable for potential HDGC families from Newfoundland in which there is no known living relative with either diffuse gastric cancer or lobular breast cancer from whom a high-quality peripheral blood DNA sample can be obtained for full CDH1 genetic screening because testing a single mutation can be readily performed on suboptimal DNA from archival tissue samples."

Source: JAMA and Archives Journals