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• *LETTERS TO THE EDITOR* •

Familial gastric cancers with Li-Fraumeni Syndrome: A case repast

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TO THE EDITOR

Although the incidence of gastric cancer has declined somewhat in recent years, it remains one of the most common cancers worldwide[1], and is the most common cancer in East Asian countries such as Korea and Japan[2]. In terms of the genetics of gastric cancer, mutations in *CDH1* (*E-cadherin*) have been associated with hereditary diffuse gastric cancer (HDGC). The first germline mutation in *CDH1* was reported in a large Maori HDGC family[1], with subsequent corroborations in Western and Asian HDGC families[3-5]. *CDH1* mutations are believed to be associated with up to 50% of HDGC families[5], but have not been linked with sporadic or intestinal types of gastric cancer[5]. Interestingly, the observed *CDH1* germline mutations differ between Western and Asian countries; the mutation frequencies are higher in Western countries, with predominately truncating germline mutations observed, whereas only a few different missense mutations have been reported in Asian countries[6]. This ethnic difference and the low frequencies of *CDH1* germline mutation in Asian populations prompted researchers to seek other susceptibility gene for Asian familial gastric cancer (FGC)[2,7]. We found a *MET* germline mutation in a FGC patient suffering from a diffuse type of gastric cancer[2], and another group reported a *MET* germline mutation in a gastric cancer patient without detailed family history information[7]. These *MET* germline mutations were also found in Korean gastric cancer patients, but the overall *MET* mutation frequencies seem to be low (1%[7] and 5%[2]), suggesting that while *MET* germline mutations may be causative in Korean or Asian gastric cancer patients, they likely do not play a major role in the development of FGC. Thus, no major FGC-related susceptibility gene has been identified in Asian countries to date.

The *TP53* tumor suppressor gene is known to cause Li-Fraumeni Syndrome (LFS), a rare hereditary clustering of malignancies including sarcoma, breast cancer, brain tumor, leukemia and adrenocortical carcinoma (Table 1)[8]. Along with these five major cancers, LFS has also been associated with a wider range of tumors, such as melanoma, Wilms' tumor, lung, gastric, and pancreatic carcinoma[8]. The definition of LFS includes a proband diagnosed with sarcoma before 45 years of age, a first-degree relative with cancer before this same age, and another first-or second-degree relative in the lineage with any cancer before this age or sarcoma at any age[9]. *TP53* germline mutations have been reported in around 80% of LFS and 40% of Li-Fraumeni-like (LFL) syndrome patients[8].

Recently, Keller *et al*., reported a *TP53* germline mutation in one German FGC patient[10]. They further performed mutational screening of *CDH1* and *TP53* in 35 FGC patients, which led to identification of two *CDH1* (one frameshift and one missense) and one *TP53* (missense) germline mutation (1 out of 34, for a 3% mutation frequency in *TP53*; only the proband was available for analysis). This novel report of a *TP53* germline mutation in one FGC patient suggested that *TP53* might play a role in the development of FGC. Based on this, Keller *et al*., recommended that the *TP53* gene should be included in genetic screening of FGC patients with a suspected genetic predisposition for the disease.

Very recently, Oliveira *et al*., reported a *TP53* germline mutation in 1 out of 10 screened FGC families from Portugal, which also has a high incidence of gastric cancer[11]. Interestingly, the Portuguese family with the *TP53* germline mutation had a family history of both FGC (three gastric cancer members) and atypical LFS (one pancreatic cancer patient and one colon cancer patient). This family had previously been described as a Li-Fraumeni kindred[12]. Based on these results, Oliveira *et al*., reiterated the suggestion of Keller *et al*., that families with an excess of gastric cancer should be considered for *TP53* mutation screening. These two reports differ from two previous studies of Japanese FGC families, in which no *TP53* germline mutations were identified[13,14].

In our lab, we screened the entire coding region of *TP53* in probands from 23 Korean FGC families. We identified a nonsense (E287X) *TP53* germline mutation in 1 (SNU-G2)

Table 1 Definition of Li-Fraumeni syndrome and familial gastric cancer subtypes (familial gastric cancer, hereditary diffuse gastric cancer, and familial intestinal gastric cancer)

	Hereditary cancer	Definition	Reference
1	Li-Fraumeni syndrome (LFS)	A proband with a sarcoma under 45 yr Plus 1st degree relative under 45 yr with any cancer Plus an additional 1st or 2nd degree relative in the same lineage with any cancer aged under 45 yr or sarcoma at any age	8
2	Familial gastric cancer (FGC)	At least two gastric cancer patients within 1st degree relatives and one patient diagnosed before the age of 50	6
2-(1)	Hereditary diffuse gastric cancer (HDGC)	(1) Two or more diffuse gastric cancer patients in 1st or 2nd degree relatives, with at least one diagnosed before the age of 50 (2) Three or more diffuse gastric cancer patients in 1st or 2nd degree relatives, indepently of age of onset	15
2-(2)	Familail intestinal gastric cancer (FIGC)	At least three relatives should have intestinal gastric cancer and one of them should be a 1st degree relative of the other two Plus at least two successive generations should be affected plus in one of the relatives, gastric cancer shoul be diagnosed before the age of 50	15

Criteria for countries with high incidence of gastric cancer.

out of the 23 screened individuals[6]. The E287X *TP53* mutation segregated with the cancer phenotype in family members from whom DNA samples were available. As there were seven individuals in this family affected with gastric cancer, we initially believed that *TP53* might be a new candidate gene for FGC. However, a thorough clinical investigation revealed that two members of this family were afflicted with brain tumors, seven with gastric cancers, two with sarcomas and one with both gastric cancer and a sarcoma. This family history is compatible with both FGC and LFS. Thus, it is highly probable that the identified *TP53* germline mutation in our family (and perhaps those investigated in the other papers) is associated with LFS regardless of FGC history.

Based on this observation, we examined the pedigree in which Keller *et al*.[10], identified their *TP53* germline mutation. This family included three gastric cancer patients, 1 individual who died of leukemia at age 17, one individual who died of liver carcinoma at age 34, and two individuals (younger brothers of the proband) for whom the causes of death were not listed. Although this family history satisfies the criteria for FGC, the family cannot be excluded from meeting the LFS criteria[8,9]. Indeed, if this family was listed as including one sarcoma patient, the family history could satisfy the classical LFS criteria[8,9].

Thus, the three recent papers[6,10,11] appear to indicate that germline mutations in *TP53* likely do not contribute significantly to the development of FGC, but are instead associated with LFS, which may be accompanied by FGC in countries with high gastric cancer incidences. As there is presently insufficient clinical data to assess the incidence and prevalence of LFS in countries with high gastric cancer incidence rates, these results are very important for directing the genetic screening and counseling of FGC families. As suggested by Keller *et al*.[10], and Oliveira *et al*.[11], *TP53* mutation screening should be performed in FGC families with LFS-related cancers, whether or not the mutation is causative of FGC or only LFS. In addition, further work will be warranted to determine more clearly whether or not *TP53* contributes to the development of FGC with LFS-related clinical symptoms.

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