Li-Fraumeni syndrome (LFS; MIM #151623), which was first described in 1969 by Li and Fraumeni [1], is a cancer predisposition syndrome associated with sarcoma and a wide spectrum of tumors. Birch et al. [2] and Eeles [3] identified several families exhibiting traits similar to LFS, but...
as these families did not exactly satisfy LFS criteria, they were designated as having Li–Fraumeni like syndrome (LFL). Classic LFS is defined as having a proband with sarcoma before the age of 45 yr, and a first–degree relative with any cancer under the age of 45 yr, and also a first- or second-degree relative with any cancer under the age of 45 yr or sarcoma at any age [1]. LFL is defined as two first- or second-degree relatives with LFS related malignancies including sarcoma, breast cancer, brain tumor, adrenal cortical tumor, or leukemia at any age [3].

TP53 is the main tumor suppressor gene associated with LFS and LFL, and over 50% of the LFS families have an identifiable TP53 germline mutation [4]. In LFL families, TP53 germline mutation rates vary from 8% to 22% according to the definition used [5]. LFS is a highly penetrant cancer syndrome, and identification of a germline mutation can confirm its diagnosis.

Here, we report a case of LFL with a germline mutation in the TP53 gene. With the patient’s consent, genetic counseling and germline mutation analysis of the TP53 gene were performed, which subsequently led to the diagnosis of another malignancy.

**CASE REPORT**

A 26-yr–old female patient with bilateral breast cancer was initially diagnosed with right breast cancer at age 24 yr, and received a right quadrantectomy with lymph node dissection and postoperative radiotherapy. One year later, a left breast mass was detected and excision of the left tumor and radiotherapy were performed. She was being treated with tamoxifen and no evidence of recurrence was detected on ultrasonography or breast MRI. Given her family history of various types of early onset cancers, she was referred to a genetic counseling clinic. Thorough review of her family history revealed multiple early onset cancers, including brain tumors, gastric cancer, and lung cancer (Fig. 1). The patient’s younger brother was diagnosed with, and died from, a brain tumor at the age of 4 yr. Her younger sister was diagnosed with gastric cancer at the age of 20 yr and died at the age of 22 yr. The patient’s older sister died of an undefined cause with ascites at the age of 11 yr. Her father died of lung cancer at the age of 36 yr, and one of her paternal uncles died of a brain tumor at the age of 10 yr. Therefore, she was clinically diagnosed with LFL. Genetic analysis of the TP53 tumor suppressor gene was performed with the patient’s consent. Leukocyte DNA was extracted using the Puregene DNA Purification kit (Gen–tra System, Minneapolis, MN, USA) according to the manufacturer’s instructions. Genetic analysis of the TP53 tumor suppressor gene was performed using direct sequencing, covering exons and exon–intron borders of exons 5, 6, 8, 9, and 11. The PCR reaction mixture (10 μL) contained 1.0 μL 10× PCR buffer (Takara, Tokyo, Japan), 0.7 μL 2.5 mM each dNTP (Takara), 0.3 μM each primer (Bioneer Corp., Cheongwon, Korea), 0.5 U Taq DNA polymerase (Takara), and 1 μL (0.5 μg) genomic DNA. The thermal cycler (Biometra T Gradient PCR, Gottingen, Germany) amplification profile used was as follows: 35 cycles of 30-sec denaturation at 95°C, 30-sec annealing at 60°C (up to 65°C), and 30-sec extension at 72°C. Amplified DNA (1.5 μL) was incubated with 2 U shrimp alkaline phosphatase and 5 U exonuclease I (USB Corp., Cleveland, OH, USA) at 37°C for 15 min. The enzymes were inactivated by incubation at 80°C for 15 min, after which the DNA was denatured at 95°C for 15 min. The presence of a PCR product was determined using agarose gel

![Fig. 1. Pedigree of the Li-Fraumeni like syndrome family. Solid symbols represent individual with tumors. Types of tumors are indicated, with ages (yr) at the time of diagnosis and death (if applicable). Asterisk (*) marks the individual analyzed and found to carry the germline TP53 mutation. Abbreviations: Dx, diagnosis; d, death; Ca, cancer.](image-url)
electrophoresis. Cycle sequencing was performed using a BigDye Terminator Cycle Sequencing Ready Reaction kit v3.0 (Applied Biosystems, Foster City, CA, USA) and an automated ABI Prism 3100 Genetic Analyzer (Applied Biosystems).

Sequencing revealed that the patient had a mutation in codon 175, resulting in an amino acid change from arginine to histidine (g.13203G > A, p.R175H) (Fig. 2). Considering the family history, an individualized cancer surveillance program, including gastroscopy and brain MRI, was recommended. The patient agreed to preventive cancer surveillance. Although she had no neurological symptoms, a huge mass on the temporal lobe was found on a brain MRI, and pleomorphic xanthoastrocytoma was pathologically diagnosed. The tumor was removed, and this procedure was followed by a radiotherapy. Despite this treatment, the residual brain tumor mass required further treatment; however, the patient decided on supportive care alone and was discharged.

**DISCUSSION**

This study revealed a 26-yr-old LFL patient with a germline TP53 missense mutation in codon 175, resulting in an amino acid change of arginine to histidine. This is the third report of LFS/LFL in Korea. The first case was reported in 1995 by Bang et al. [6] with a family history of early onset breast cancer with p53 germline mutation confirmed in the proband and her sister. The second report was in a hereditary diffuse gastric cancer family with LFS related phenotype [7]. The mutations found in all three cases were different and the mutation of this case is in the L2 loop that binds the minor groove of DNA and has been found to be deleterious in *in silico* analysis using both Align–GVGD and SIFT methods [8]. It is one of the most common mutations reported, and is found in 20 Li–Fraumeni families according to the International Agency for Research on Cancer TP53 database R12 release [8]. The present case is also consistent with a study by Olivier et al. [9], in which brain tumors were associated with missense *TP53* mutations located in the DNA–binding loop.

Although the mutation in the case was one of the most common mutations found in LFL/LFS, this case proposes many key issues in genetic testing for familial cancer syndrome patients. As can be seen in this case, the timing of genetic screening is crucial. Despite the family history of multiple early onset cancers, the patient was offered testing only after the diagnosis of bilateral cancers. There is evidence to suggest that a prophylactic mastectomy in women with a high risk of breast cancer is beneficial, and may have been of benefit to the patient in this report [10]. Several cases of radiation-induced secondary malignancies have been reported, and there are many reviews on the controversial effects of radiation in LFS patients [11–13]. If the mutation status had been revealed, the patient and the medical staff may have chosen an alternative to radiotherapy after the diagnosis of the right breast cancer.

Another issue is the genetic testing of family members of a known familial cancer syndrome patient. Testing of other family members who are at risk of carrying the same mutation may be helpful in early diagnosis and treatment. This report shows a family of index case with two members...
with brain tumors and one member with breast cancer at the time of genetic counseling. Since gastric cancer and lung cancer have not yet been defined as LFL malignancies, only three individuals, including the proband, are included in LFL-defining criteria. However, other cancers that have not yet been classified as typical LFL malignancies might still be considered as a phenotype in LFL or LFS. This is supported by the discovery of a TP53 germline mutation in a family with hereditary diffuse gastric cancer in Korea [7]. Although the genetic testing was not performed in other family members, genetic counseling was done informing the possibilities of their mutation status and their options following the testing.

The last is the issue of surveillance after genetic screening. Due to the lack of effective screening, and the complex nature of the disease, Chompret et al. [14] suggested that individuals be offered TP53 analysis if they fulfill certain criteria. Although the effectiveness of genetic testing and surveillance have not yet been proven with respect to LFS or LFL, many clinicians conduct surveillance strategies according to their policy [15]. In this case, a huge brain tumor was found incidentally after the surveillance measure, which enabled surgery and treatment.

Our experiences with the patient described herein, which highlight the impact of genetic testing in patients suspected of familial cancer syndrome, indicate that such patients should be given a genetic counseling by professionals before and after a genetic testing.

REFERENCES

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