pathologic stage of IA. Her neuropsychiatric symptoms failed to abate despite surgery and a course of intravenous immunoglobulins. Fourteen days postoperatively, she was started on adjuvant chemotherapy with a standard chemotherapeutic regime of BEP, receiving a total of three cycles. Her dystonia became less prominent rapidly after initiation of her first cycle, but it was only after 20 days after commencement of chemotherapy that she regained orientation and was able to answer questions in a relevant and appropriate manner. She returned to work four months after completion of chemotherapy.

These two cases highlight the role of chemotherapy as an adjunct to surgery in a multimodality approach to paraneoplastic encephalitis associated with teratoma. In the first patient, the temporal association is definitive where neuropsychiatric symptoms only developed after the teratomas were resected. These symptoms resolved completely following chemotherapy. Given that tumour foci were identified on the omentum and in the peritoneal fluid, it is conceivable there may have been residual disease after surgery resulting in a delayed onset of encephalitis. This would further support the role of chemotherapy as an adjunct to surgery. In the second patient, since both surgery and intravenous immunoglobulin was administered prior to chemotherapy, one cannot exclude the possibility that her improvement may have represented a delayed effect of treatment. However, a strong temporal association between initiation of chemotherapy and symptom improvement was noted.

In a review of patients reported to have paraneoplastic encephalitis associated with immature ovarian teratomas in the English literature (Table I), only three of the ten patients received chemotherapy, with a fourth receiving cyclophosphamide only [1–6]. The grade and stage of the disease as well as the details of treatment were however not reported for all ten patients so it is unclear whether chemotherapy would have been recommended [7,8]. The current difficulty in establishing ideal treatment modalities lies in the small number of patients that have been identified to date and further reports may be helpful to determine this.

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Somatic mutation of GNAQ gene is rare in common solid cancers and leukemias

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To the Editor

Guanine nucleotide-binding proteins are a family of proteins that couple cell surface receptors to intracellular signaling pathways. Receptor activation catalyzes the exchange of GTP for GDP bound to the inactive G protein alpha subunit. The G protein subunits are capable of regulating various cellular functions [1,2]. G-alpha-q (GNAQ) is the alpha subunit of one of the heterotrimeric GTP-binding proteins that mediates stimulation of protein kinase C signaling. GNAQ contributes to heart development, platelet functions, and skin color formation [1–3].

Recently, Van Raamsdonk et al. [3] analyzed a broad spectrum of benign and malignant melanocytic neoplasia for the detection of *GNAQ* somatic mutations. They found a recurrent somatic point mutation of *GNAQ* (p.Q209L) in malignant blue nevus (50%), blue nevus (83%), Ota nevus (6%), melanoma on skin with chronic sun-induced damage (4%), and ocular malignant melanoma (46%). Functionally, the *GNAQ* p.Q209L mutation enhanced anchorage-independent cell growth *in vitro* and tumorigenicity *in vivo* [3]. The p.Q209L mutation activated protein kinase C signaling, which subsequently activated MAP kinase pathway [3]. Because MAP kinase signaling is constitutively activated not only in malignant melanomas but also in many human cancers [4], it could be hypothesized that the *GNAQ* p.Q209L mutation could be responsible to the MAP kinase signaling activation in other cancers besides malignant melanomas as well. To explore this issue, in the present study, we analyzed the *GNAQ* p.Q209L mutation in common solid cancers and leukemias.

For this, we analyzed 667 cancer tissues from Korean patients (breast carcinomas (n = 47), colon carcinomas (n = 79), lung carcinomas (n = 47), stomach carcinomas (n = 47), esophageal squamous cell carcinomas (n = 68), hepatocellular carcinomas (n = 76), hepatoblastomas (n = 56), prostate adenocarcinomas (n = 47), urothelial carcinomas (n = 28), ovarian carcinomas (n = 80), squamous cell carcinomas of uterine cervix (n = 17), skin squamous cell carcinomas (n = 6) and renal cell carcinomas (n = 16), and malignant mesotheliomas (n = 6) and acute leukemias (n = 47)) by a polymerase chain reaction (PCR)- single strand conformation polymorphism (SSCP) assay. The colon carcinomas originated from cecum (n = 2), ascending colon (n = 17), transverse colon (n = 4), descending colon (n = 4), sigmoid colon (n = 20) and rectum (n = 32). The gastric carcinomas consisted of 18 diffuse-type, 15 intestinal-type and 14 mixed-type gastric adenocarcinomas by Lauren's classification, and seven early and 40 advanced gastric carcinomas according to the depth of invasion. The breast carcinomas consisted of seven ductal carcinomas *in situ* and 40 invasive ductal carcinomas. The ovarian carcinomas consisted of 45 serous and 35 mucinous adenocarcinomas. The NSCLC samples consisted of 25 adenocarcinomas and 22 squamous cell carcinomas. We analyzed the primary tumors, but not the metastatic lesions. In solid tumors, malignant cells and normal cells were selectively procured from hematoxylin and eosin-stained slides using a 30G1/2 hypodermic needle affixed to a micromanipulator, as described previously [5]. The content of the tumor cells in the microdissection was 85–97%. DNA extraction from the microdissected tissues was performed by a modified single-step DNA extraction method by proteinase K treatment [5]. Genomic DNA each from tumor cells and normal cells from the same patients were amplified by PCR with a primer pair covering the mutation (p.Q209L) sequence in exon 5 of human *GNAQ* gene. The primer sequences of *GNAS* were as follows (forward and reverse, respectively): 5′-attttccctaagtttgtaagtag-3′ and 5′-cagtgtatccatttttcttctc-3′. Radioisotope ([^{32}P]dCTP) was incorporated into the PCR products for detection by autoradiogram. The PCR products were subsequently displayed in SSCP gels. Other procedures of PCR and SSCP analysis were performed as described previously [5].

On the SSCP autoradiograms, all of the PCR products from the cancers were clearly seen. However, the SSCPs from them did not reveal any aberrantly migrating band compared to wild-type bands from the normal tissues, indicating there was no evidence of the somatic mutation of *GNAQ* in the cancers. To confirm the SSCP results, we repeated the experiments twice, including tissue microdissection, PCR and SSCP to ensure the specificity of the results, and found that the data were consistent. We analyzed the GNAQ mutation in 100 cancers (30 breast, 30 colon, 20 gastric and 20 leukemias) used in this study by direct sequencing as well as by SSCP, and no additional mutation was detected by the direct sequencing.

One of the main concerns in cancer genetics is as to whether any mutation found in a cancer is common in other cancer types. For example, *EGFR* mutation is specific to few cancer types [6], whereas *K-RAS* mutation is common to many cancer types [7]. As a possible mechanism of MAP kinase signaling activation in common human cancers, we analyzed *GNAQ* mutation in a variety of human cancers. However, we detected no *GNAQ* p.Q209L mutation in the cancers. Compared to the high incidences of the *GNAQ* mutation in the melanomas and nevi [7], the incidence in the cancers analyzed in this study was significantly low (Fisher's exact test, $p < 0.05$). Our data indicate that the MAP kinase signaling activation frequently observed in the cancer types may not be a result of the *GNAQ* mutation. The discovery of the *GNAQ* p.Q209L mutation as an oncogene offered an opportunity for developing therapeutic

as well as diagnostic tools for human cancers. From our observation, however, such approaches may be restricted to melanocytic neoplasia.

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Absence of oncogenic AKT1 E17K mutation in prostate, esophageal, laryngeal and urothelial carcinomas, hepatoblastomas, gastrointestinal stromal tumors and malignant meningiomas

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To the Editor

AKT1, which contains a pleckstrin homology (PH) domain, is a serine/threonine protein kinase. Mounting evidence indicates that activation of AKT1 is important in cancer development. An activating *AKT1* mutation was recently identified in human breast (8.2%), colorectal (5.9%) and ovarian cancers (2.0%) [1]. The *AKT1* mutation was a missense mutation that substituted an amino acid (E17K) in the PH domain. The *AKT1* E17K mutation indu ces cellular transformation *in vitro* and produces leukemias in mice [1].

Because of the importance of AKT signaling activation in cancer development, following studies analyzed the *AKT1* E17 mutation in a wide range of human cancers [2–5]. They found the *AKT1* E17 mutation in breast, lung, and colon cancers, and malignant melanoma, but not in other cancers, including pancreas, liver, stomach cancers, and leukemias [2–5]. To see whether the *AKT1* E17 mutation occurs in other cancers, we analyzed the *AKT1* E17 mutation in cancers where the mutation has not been studied.

For this, we analyzed the *AKT1* E17 mutation in methacarn-fixed tissues of 134 prostate adenocarcinomas, 61 esophageal squamous cell carcinomas, 31 laryngeal squamous cell carcinomas, 26 urothelial carcinomas, 38 hepatoblastomas, 22 gastrointestinal stromal tumors (GIST) and 10 malignant meningiomas by a polymerase chain reaction (PCR)-single strand conformation polymorphism (SSCP) assay. All of the patients of the cancers were Koreans. In the tumors, malignant cells and normal cells were

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