Review Article

Inherited lung cancer syndromes targeting never smokers

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Abstract: Lung cancer is the leading cause of cancer death worldwide. Most of lung cancers develop sporadically and thus inherited lung cancers are rare. Several reports show that germline mutations in the kinase domain of epidermal growth factor receptor (*EGFR*) such as R776G, R776H, T790M, V843I and P848L, predispose to develop lung cancer. Most lung cancer cases with germline *EGFR* T790M mutations had secondary *EGFR* somatic mutations. Never smokers with germline *EGFR* T790M mutations develop lung cancer more frequently than ever smokers. In addition, germline *EGFR* T790M mutations favored female gender. Therefore, germline *EGFR* T790M mutations result in a unique inherited lung cancer syndrome targeting never smokers. The authors previously reported a Japanese familial lung cancer pedigree with germline mutations in the transmembrane domain of human epidermal growth factor receptor 2 (*HER2*). The female proband and her mother in this pedigree, who were light or never smokers, developed multiple lung adenocarcinomas, and had germline *HER2* G660D mutations. They had no *EGFR* somatic mutations or other genes known to cause lung cancers. Although we know only one pedigree with germline *HER2* mutations, these mutations may also cause inherited lung cancers targeting female never smokers. Based on our *in vitro* analyses, we administered *HER2* inhibitor afatinib to the proband and achieved partial response. These lung cancers arising from germline mutations of receptor tyrosine kinases such as *EGFR* and *HER2* may have different features from those with sporadic mutations.

Keywords: Inherited lung cancer syndromes; epidermal growth factor receptor (*EGFR*); human epidermal growth factor receptor 2 (*HER2*)

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Introduction

Lung cancer is one of the refractory malignancies and the leading cause of cancer death worldwide (1-3). This disease is often diagnosed at the advanced stages, in which the treatment is less effective, and thus it still has a poor outcome. To improve a worse prognosis, various researches have been conducted. One of the significant research progress is the discovery of the somatic activating mutations in the tyrosine kinase domain of epidermal growth factor receptor (*EGFR*) (4-6). These mutations mainly consist of exon 19 deletion and exon 21 point mutation (L858R), and frequently occur in adenocarcinoma, female, East Asian, and never smokers (7). Lung cancers with *EGFR* activating mutations initially well respond to EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib (4-6). EGFR-TKIs showed prolonged disease-free survival in phase III clinical trials (8-10). However, the tumors eventually acquire the resistance to TKIs, which is the issue to be overcome. One of the major mechanisms for the acquired resistance to TKIs is a secondary *EGFR* mutation T790M in exon 20 (11,12). T790M mutations

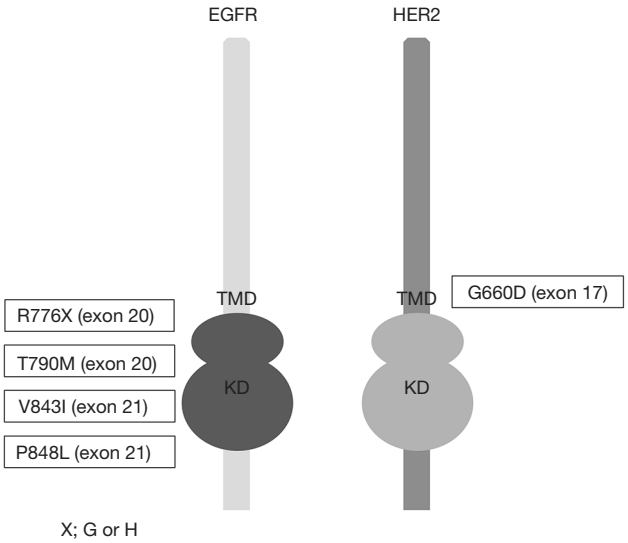

Figure 1 Schema of EGFR and HER2. Germline *EGFR* R776X (X; G or H), T790M, V843I and P848L mutations reported in lung cancers are located in the kinase domain. Germline *HER2* G660D mutation is located in the transmembrane domain. TMD, transmembrane domain; KD, kinase domain.

may exist in treatment-naïve tumors, and the clones with T790M are selected in the course of the TKI treatment (13). More recently, immune checkpoint inhibitors have brought change to the treatment of lung cancer and showed the promising therapeutic effect (14). In this manner, the treatment of lung cancer has been drastically changed. However, to improve the outcome of lung cancer more, it is necessary to further understand molecular oncology, and one of the approaches may be the comprehension of cancer susceptibility including inherited germline alterations.

Although vast majority of malignancies from various organs develop sporadically, we sometimes encounter inherited cancer syndromes, such as hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), hereditary breast and ovarian cancer syndrome (HBOC), Li-Fraumeni syndrome, retinoblastoma, and multiple endocrine neoplasia (15-20). Compared to other organs, most of lung cancers develop sporadically and inherited lung cancers are rare. While inherited lung cancers are rarely observed, several reports investigated genetic susceptibility to inherited lung cancers (21-26). Those previous reports describing inherited lung cancers did not much focus on the relationship between genetic factors and smoking status.

In this review, we introduce the reported inherited lung cancer pedigrees with germline mutations, and discuss the features of such inherited lung cancers, especially smoking status, sex, and ethnicity.

Driver mutations in lung cancer

Malignant tumors develop due to the accumulation of the mutations in a portion of genes, which provide growth advantage. Systematic resequencing of cancer genomes led to the discovery of the new cancer-related genes. While many somatic mutations are observed in cancers, most of them are likely to be "passengers", which do not contribute to carcinogenesis. On the other hand, "driver" mutations exist in a subset of somatic mutations, which are responsible to develop cancers (27). In lung cancer, several gene mutations are reported to be drivers. In addition to *EGFR* described above, mutations of *KRAS*, *ALK*, human epidermal growth factor receptor 2 (*HER2*), *BRAF*, *PIK3CA*, *AKT1*, *MAP2K1* and *MET* are reported to be drivers in lung cancer (28). These alterations are potential therapeutic targets, and molecular targeting drugs such as EGFR-TKI are developed.

Previously reported inherited lung cancer pedigrees with germline *EGFR* mutations

As described above, inherited lung cancers are rarely observed. However, several reports investigated genetic susceptibility to inherited lung cancers, and the reports describing *EGFR* germline mutations in lung cancer pedigrees draw the attention of us (29-37). In addition to these reports, lung cancer cases with germline *EGFR* mutations are reported, although the evident familial history of lung cancers are not obtained (38-40). Reported *EGFR* germline mutations are R776G, R776H, T790M, V843I and P848L, which are all located in the kinase domain of *EGFR* (*Figure 1*), and notably, T790M mutations are frequently reported (29,31,32,34,35,37) (*Table 1*). In the pedigrees with *EGFR* germline mutations including T790M, many of affected family members develop secondary somatic *EGFR* activating mutations such as exon 19 deletion and L858R. Presumably, T790M mutation itself is a weak oncogene. However, when secondary somatic mutations occur, the oncogenic power of combined germline and somatic mutations should become enormous. Gazdar et al. studied the pedigrees with germline *EGFR* T790M mutations in detail. Several patients with germline T790M mutations had multiple lung tumors, and computed tomography

Table 1 Reported lung cancers with germline RTK mutations

Author	Year	Germline mutation	Secondary somatic mutation	Ethnicity
Bell	2005	*EGFR* T790M	*EGFR* L858R, del L747-T751, G719A	Caucasian
Sequist	2006	*EGFR* P848L	No *EGFR* mutations	N/A
Ikeda	2008	*EGFR* V843I	*EGFR* L858R, L861Q	East Asian
Prudkin	2009	*EGFR* T790M	No *EGFR* mutations	N/A
Girard	2010	*EGFR* T790M	*EGFR* L858R	East Indian/Caucasian
Tibaldi	2011	*EGFR* T790M	*EGFR* del E746-A750	Caucasian
Ohtsuka	2011	*EGFR* V843I	*EGFR* L858R	East Asian
Centeno	2011	*EGFR* R776G	*EGFR* L858R	N/A
Oxnard	2012	*EGFR* T790M	*EGFR* L858R, exon 19 del	N/A
van Noesel	2013	*EGFR* R776H	*EGFR* G719A, G719S	Caucasian
Gazdar	2014	*EGFR* T790M	*EGFR* L858R	Caucasian
Prim	2014	*EGFR* V843I	*EGFR* L858R	Caucasian
Prim	2014	*EGFR* P848L	No *EGFR* mutations	Caucasian
Yamamoto	2014	*HER2* G660D	No *EGFR* mutations	East Asian

RTK, receptor tyrosine kinases; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2.

(CT) scans of unaffected carriers revealed multiple ground glass nodules of uncertain etiology, implying that they have multiple preinvasive lesions (29). They also showed the association of sex and smoking status with developing lung cancer, indicating that germline T790M mutations targeted female never smokers, different from sporadic lung cancers, most of which target ever smokers (29). Interestingly, all the affected family members with germline T790M mutations are Caucasians or East Indians, that is, the absence of reported T790M germline mutations in East Asian ethnicity, whereas sporadic *EGFR* mutations mainly occur in East Asians. Reported affected members with germline *EGFR* V843I mutations in 2 reports are East Asians and another report shows a Caucasian (*Table 1*).

Germline mutation of *HER2* in a Japanese pedigree of inherited lung cancer

There is a possibility for the oncogenes other than *EGFR* to cause inherited lung cancers. We previously reported a family of Japanese descent with inherited lung cancers, in which germline *HER2* mutations were detected (41). The proband was 53-year-old female at the time of the analysis with multiple lung adenocarcinomas in the bilateral lungs. She was a light smoker with 1.2-pack-year history of smoking. In addition, normal-appearing lung parenchyma obtained from a lobectomy in the proband revealed innumerable small preinvasive lesions, implying the presence of precancerous changes throughout the lung. Her mother, who was a never smoker, also suffered from multiple lung adenocarcinomas. We performed exome sequencing using tumor and blood samples of affected and unaffected family members. Novel germline *HER2* mutations G660D were detected in the transmembrane domain, although reported *HER2* somatic mutations are located in the kinase domain (42,43). In contrast to the lung cancers with germline *EGFR* mutations, we were not able to detect secondary somatic mutations of the genes known to cause lung cancers including *EGFR* (*Table 1*). We also confirmed no copy number gain of *HER2* in the examined tumors. Based on our *in vitro* analyses (44), we administered HER2 inhibitor afatinib to the proband and achieved partial response (45). We tested the mutational status of *HER2* using the blood sample for the proband's daughter, who received the genetic counseling before testing and after the results were obtained. She also had germline *HER2* G660D mutation. Her tobacco exposure was 4.5 pack-years, indicating a light smoker. Computed tomography (CT) scan of the chest for her at the age of 30 is shown in *Figure 2*. Multiple ground-glass nodules in bilateral lungs

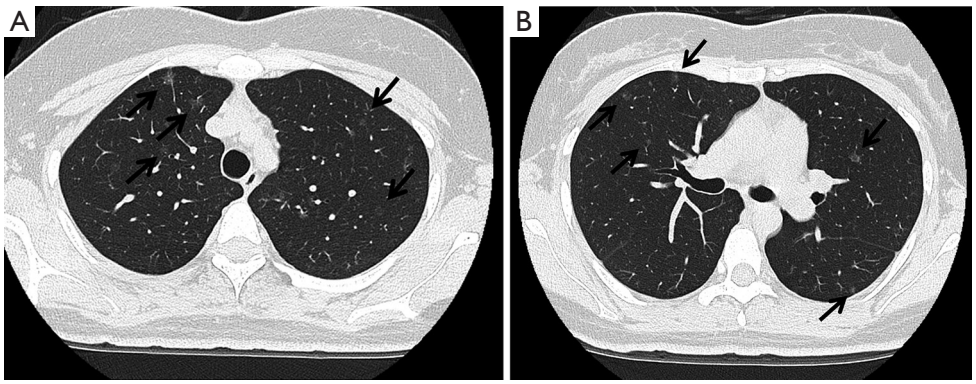

Figure 2 Computed tomography (CT) scan of the chest of the proband's daughter in the pedigree with germline *HER2* G660D mutation at the age of 30. Multiple ground-glass nodules in bilateral lungs are observed.

were observed, similar to the carriers with germline *EGFR* T790M mutations. In this pedigree, among nine lung cancer patients, female patients are six, accounting for 66.7% (41). Although information of smoking status in this pedigree is limited to only the proband (with lung cancer), her mother (with lung cancer) and her daughter (carrier with multiple ground glass nodules), those three members are never or light smokers. Therefore, there is also the possibility that germline *HER2* transmembrane mutations target female never smokers, same as germline *EGFR* T790M mutations.

Germline mutations other than *EGFR/HER2* that predispose to lung cancer

There are several reports that describe germline mutations other than *EGFR/HER2*, which predispose to lung cancer. Germline mutation of BRCA-associated protein-1 (BAP1) has been associated with the high risk for malignant mesothelioma, lung adenocarcinoma, uveal melanoma, and cutaneous melanoma (46). Germline *BRCA1* mutation was detected in a patient with non-small cell lung cancer who responded to cisplatin/gemcitabine plus HSP90 inhibitor DEBIO0931 (47). Rare variant *BRCA2 K3326X* was reported to be associated with squamous cell lung cancer (48). A familial *CDKN2A* mutation R112dup has been associated with an increased risk of lung, head and neck and gastroesophageal cancer in patients who smoke (49). *LKB1* is mutated in the germ-line of patients with the Peutz-Jeghers syndrome, which have an increased incidence of several cancers including lung cancers (50). Germline *SFTP2A* mutation is reported to cause familial idiopathic pulmonary fibrosis and lung cancer (51).

Next generation sequencing technology makes it possible to perform comprehensive analysis of genome in high speed. Some studies successfully narrowed down the several candidate genes (22,52). While functional analysis is critical, accumulation of these knowledge will lead to identification of causative genes, which results in elucidating carcinogenesis of lung cancer as well as in developing the new therapeutic strategies of lung cancer.

Single nucleotide polymorphisms (SNPs) and susceptibility of lung cancer

Single nucleotide polymorphism (SNP) is a variation at a single position in the genome, if the frequency of the variation is more than 1% in the population. Several SNPs are reported to be associated with the susceptibility of lung cancer. Genome wide association studies (GWAS) revealed that SNPs at 15q25, which is the site of nicotinic acetylcholine receptor subunit genes *CHRNA5*, *CHRNA3*, *CHRNB4*, were strongly associated with lung cancer (53). Lan and colleagues revealed three susceptibility loci at 10q25.2 (rs7086803), 6q22.2 (rs9387478) and 6p21.32 (rs2395185) in Asian women who never smoked. They also observed that no evidence of association for lung cancer at 15q25 in never-smoking women in Asia (54). Wang and colleagues reported that SNPs at 5p15.33-*TERT* (rs2736100) and 5p15.33-*CLPTM1L* (rs4975616) were associated with lung cancer in never smokers (55). Another GWAS study reported that 10 SNPs including newly detected two loci, 17q24.3-*BPTF* (rs7216064) and 6p21.3-*BTNL2* (rs3817963), were associated with lung adenocarcinoma risk in never-smoking Asian women. Of these 10 SNPs, three SNP markers *TERT*, *TP63* and 9p21.3 were also significantly associated with lung adenocarcinoma

risk in Western never-smokers. Among Western smokers, only two out of 10 SNPs (*TERT* and *TP63*) were significantly associated with lung adenocarcinoma risk (56).

Conclusions

Germline *EGFR* T790M mutations cause rare and characteristic inherited lung cancer syndromes, which target female never smokers. Although only one pedigree is so far reported regarding inherited lung cancer syndrome with germline *HER2* mutations, this syndrome may also target female never smokers. Because unaffected family members in these pedigrees have an increased risk to develop lung cancer, it is necessary to follow them deeply by the CT scan of the chest. Even though inherited lung cancers are rare, these molecular characteristics may be contributory to understanding the pathogenesis of lung cancer, and thus they also may shed light on the elucidation of sporadic lung cancers.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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