Germline EGFR mutations in lung cancer (Review)

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Abstract. Lung cancer is the leading cause of cancer-related death and familial lung cancer is a potential contributing factor. Epidermal growth factor receptor (EGFR) mutations are important events in carcinogenesis. The present study summarized the common germline mutations of EGFR, including T790M, V843I, R776H and P848L, and provided detailed information regarding each mutation site and potential treatment strategies. Individuals with germline mutations may develop lung cancer upon exposure to environmental stimuli such as smoking, air pollution or radiological contamination, or due to the occurrence of another somatic mutation. The present study recommends regular physical examinations as well as population-wide germline mutation screening for early detection and diagnosis of lung cancer.

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1. Introduction

Lung cancer was the most prevalent cause of cancer-related death (18.4% of total cancer deaths) and the most widely diagnosed (11.6% of total cancer cases) worldwide in 2018 (1). While the etiology of lung cancer remains to be fully elucidated, some of the well-established causes include tobacco use, environmental pollution and second-hand smoking (2). Approximately 8% of lung cancer cases are linked to a genetic predisposition to the disease. Multiple individuals diagnosed with lung cancer in a related family is referred to as familial lung cancer (FLC) (3). FLC occurs in the offspring of parents who carry lung cancer-linked genes. As a result, the affected individuals pass on their predisposition to lung cancer to future generations by inheriting a *de novo* autosomal dominant or X-linked germline mutation.

The majority of FLC cases occur due to germline mutations, which may include changes in the number of chromosomes (triploidy and aneuploidy) or changes in gene dosage due to duplications or deletions ranging in size from a small number of base pairs to megabases (4). Mutations may occur as duplications or deletion in microsatellites, minisatellites and chromosomes that have been remodeled via retrotransposition, translocation or inversion (4). Previous research into germline mutation has revealed that P53, von Hippel-Lindau, retinoblastoma, breast cancer-associated gene 1 (BRCA1) and BRCA2 act as 'driver mutations' in carcinogenesis. Germline mutations represent a predisposition to cancer, enabling the identification of individuals who are at a higher risk of inheriting these mutations (high-risk population). Furthermore, germline mutations may facilitate the development of novel biomarkers for diagnosis and targeted therapy (2). Tang *et al* (5) reported that epidermal growth factor receptor (EGFR) mutations are commonly observed in the normal bronchial and bronchiolar epithelia of patients with EGFR mutant lung adenocarcinomas and confirmed that EGFR mutations are early events in the tumor formation process. Furthermore, Arteaga (6) demonstrated that EGFR signaling is necessary for the development of lung adenocarcinomas in transgenic mice. Therefore, the present review aimed to summarize the germline mutations of EGFR in lung cancer and elucidate the possible underlying mechanisms.

2. Germline mutation of EGFR T790M

The T790M substitution somatic mutation at exon 20 is considered the primary cause of EGFR-tyrosine kinase

inhibitor (EGFR-TKI) acquired resistance in ~60% of patients with lung cancer treated with first-generation EGFR-TKIs (7). However, the germline T790M mutation is rare, found in only 1% of patients with lung cancer whose EGFR gene has been sequenced, and in ~50% of patients who have baseline EGFR T790M in their pretreatment tumor samples (8). Furthermore, T790M has been linked to familial non-small cell lung cancer (NSCLC) (7) and in a population of never-smoking women who carry the T790M germline mutation, there is a 31% probability of developing lung cancer.

A study of 627 Japanese patients with lung cancer found no T790M germline mutations, despite EGFR mutations being present in 33.3% of patients (209/627) (9). These findings are consistent with a gene analysis study of 503 patients with lung cancer in the US, which found only five patients with the T790M germline mutation (9). In addition, no patients with a T790M germline mutation were identified in the 1,000 Genomes Project databases or the genomes of 6,503 individuals from the National Heart Lung and Blood Institute GO Exome Sequencing Project. Another study performed peripheral blood screening on 369 non-smoking patients with lung adenocarcinoma and discovered only two patients with the germline T790M mutation (10). In 52 families with high susceptibility to lung cancer and 237 probands with FLC, no germline T790M mutation was observed, while in the two cohorts, 86% had a smoking history (11,12). Therefore, the prevalence of the germline T790M mutation in the general population is ~0.5-1/7,500 individuals (13). Further prospective evaluation of patients with lung cancer and baseline EGFR T790M mutation is recommended to better understand familial penetrance, lifetime lung cancer risk and germline prevalence.

To date, ~10 cases of germline EGFR T790M mutations have been reported. Vikis *et al* (11) previously sequenced the germline EGFR T790M mutation of 237 families with a predisposition toward lung cancer but the mutation was not detected. This suggests that this type of germline mutation is rare, even in families with a genetic predisposition toward lung cancer. Adenocarcinomas are the pathological types that exhibit the germline T790M mutation, which are generally more common in females (6:3, female/male). In a study by Gazdar *et al* (9), the median age of patients with lung cancer with a T790M germline mutation was 63 years, with the youngest proband being 29 years old. To the best of our knowledge, prior to a study by Lu *et al* (14), there were no reports of families of East Asian origin with the germline T790M mutation. Lu *et al* (14) reported a case of a Chinese patient among 5,675 EGFR-positive patients. Smoking was not associated with the development of lung cancer in people with T790M germline mutation. Of the 10 cases examined, only two were identified to have a history of smoking. It has been hypothesized that the germline EGFR T790M mutation is a weak oncogene that requires a common activating EGFR mutation, such as L858R, to induce lung cancer development. Mäkinen *et al* (15) used microdissection, a targeted panel (a hybrid-capture and massively parallel sequencing assay) and whole-exome sequencing to analyze multiple foci of atypical adenomatous hyperplasia *in situ*, invasive components of lung adenocarcinoma, normal lung tissue and whole blood from patients at the molecular level. Their findings revealed that each neoplastic lesion exhibited a secondary somatic EGFR mutation, namely L858R or L861Q (15). However, conventional chemotherapy may be utilized as the primary treatment for patients with the germline T790M mutation, as two sisters who were administered TKI exhibited partial responses (Table I) (16-18).

3. Germline mutation of EGFR V843I

Exon 21 of the EGFR gene harbors the V843I mutation (19). Initially, V843I was not recognized as a germline mutation until it was reported in a study aimed at determining the feasibility of EGFR mutation analysis in needle biopsy/aspiration paraffin-fixed specimens (19). Subsequently, Ikeda *et al* (20) presented the first evidence that V843I is a germline mutation in a study involving a 70-year-old female with multiple lung adenocarcinomas and family members with lung cancer. The patient had a germline EGFR V843I mutation and additional mutations, L861Q and L858R, were found in all examined specimens (20). The authors proposed that the V843I mutation causing lung cancer was based on the 'two-hit theory', which suggests that tumors may develop from normal tissue with congenital (first) mutations after acquiring a second mutation.

To date, four cases of germline EGFR V843I mutations have been reported (21) (Table II). Of note, three of the four patients with germline EGFR V843I mutations had a second mutation, except for patient no. 3. Ohtsuka *et al* (21) presented the case of patient no. 2 and revealed that the somatic secondary L858R mutation occurred nonrandomly in *cis* to the germline V843I mutation. By conducting growth inhibition assays of the tumor cells obtained from the pleural effusion of patient no. 2, the author concluded that the germline V843I mutation was associated with TKI resistance, similar to the germline T790M mutation (21,22). Patient no. 3 underwent three different types of therapy, including erlotinib, with no success. The researchers used computer-aided approaches to model the EGFR ATP catalytic domain in a complex with ATP, gefitinib and erlotinib to further demonstrate that the germline mutation V843I is associated with EGFR-TKI resistance (23). By contrast, patient no. 4 exhibited sensitivity to erlotinib and the effectiveness lasted for 9 months (24). Thus, three of the four reported cases of the germline V843I mutation exhibited EGFR-TKI resistance. Recently, Song *et al* (25) reported that osimertinib therapy was effective in patients with NSCLC and the germline EGFR V843I mutation. However, due to the small number of cases included, the finding that third-generation targeted drugs are effective for V843I cannot be generalized. Therefore, further research studies are required to confirm the preliminary findings.

However, the underlying mechanism by which the germline V843I mutation causes lung cancer remains elusive. One possible mechanism is that the V843I mutation causes EGFR gene instability, which then predisposes cells to additional mutations, such as L858R, L861Q and L858R, all of which may collectively cause tumorigenesis. However, the precise mechanism requires further investigation.

4. Germline mutation of EGFR R776H

In 2013, a new germline mutation, R776H, was discovered in a Caucasian mother and daughter following the discovery of two germline-transmitted EGFR variants linked to lung cancer (26). The mother's right hilar tumor was diagnosed as squamous cell carcinoma, while the daughter's right-sided lung cancer was also determined to be squamous cell carcinoma. A codon 776

Table I. Summary of patients with lung cancer exhibiting an EGFR T790M mutation.

First author, year	Sex (M/F)	Smoking history	Family cancer history	Pathology	TNM stage	Secondary somatic mutation	Ethnicity	Effective for treatment?		(Refs.)
								EGFR-TKI	Chemotherapy	
Bell, 2005	M	Yes	Yes	Unknown	Unknown	EGFR L858R, delL747-T751, G719A	Caucasian	Yes (gefitinib)	No	(16)
Bell, 2005	M	Unknown	Yes	Unknown	Unknown	EGFR G719A	Caucasian	Unknown	Unknown	(16)
Prudkin, 2009	F	No	Not mentioned	2 nodes are adenocarcinomas, and 1 node is large-cell neuroendocrine carcinoma	Unknown	No	N/A	Unknown	Unknown	(17)
Girard, 2010	F	No	Yes	Mixed adenocarcinoma with acinar and bronchioloalveolar features	Unknown	EGFR L858R	East Indian/ Caucasian	Unknown	Unknown	(10)
Girard, 2010	M	No	Yes	Poorly differentiated acinar and solid adenocarcinoma	IV	EGFR L858R	European	Unknown	Unknown	(10)
Tibaldi, 2011	F	No	Yes	Lung adenocarcinoma	Unknown	EGFR del E746-A750	Caucasian	Yes (gefitinib, partial response for 9 months)	Yes (first line, stable for 6 months)	(18)
Tibaldi, 2011	F	No	Yes	Poorly differentiated acinar and solid adenocarcinoma	IIIb	Unknown	Caucasian	Yes (gefitinib, partial response for 45 months)	Yes (first line, stable for 12 months)	(18)
Oxnard, 2012	F	No	Unknown	Lung adenocarcinoma	Advanced lung cancer	EGFR L858R, exon 19 del	NA	No	No	(8)

Table I. Continued.

First author, year	Sex (M/F)	Smoking history	Family cancer history	Pathology	TNM stage	Secondary somatic mutation	Ethnicity	Effective for treatment?		(Refs.)
								EGFR-TKI	Chemotherapy	
Gazdar, 2014	F	Yes	Yes	Adeno-carcinoma (bilateral preneoplastic and preinvasive lesions)	Unknown	EGFR L858R	Unknown	Unknown	Unknown	(9)
Vikis, 2007	M	Unknown	Yes	Lung adeno-carcinoma	IV	EGFR G719S	Chinese	Unknown	Unknown	(11)
Mäkinen, 2021	M	Yes	No	Lung adeno-carcinoma	IV	EGFR L858R	Chinese	Yes (icotinib)	Unknown	(15)
Mäkinen, 2021	F	Yes	Yes	Lung adeno-carcinoma	NA	L861Q, G719A	Chinese	Yes (icotinib)	Unknown	(15)

NA, information not available; M, male; F, female; TKI, tyrosine kinase inhibitor.

Table II. Summary of patients with lung cancer exhibiting an EGFR V843I mutation.

First author, year	Sex (M/F)	Smoking history	Family cancer history	Pathology	TNM stage	Secondary somatic mutation	Ethnicity	Effective for treatment		(Refs.)
								EGFR-TKI	Chemotherapy	
Ikeda, 2008	F	Unknown	Yes	3 nodules AD; 4 nodules BAC; 3 lesions AAH	T1N1M0 (stage IIA)	EGFR L858R, L861Q	East Asian	Not used	Unknown	(20)
Ohtsuka, 2011	F	Unknown	No	Lung adeno-carcinoma	T4N2M1 (stage IV)	EGFR L858R	East Asian	No (gefitinib, erlotinib)	No	(21)
Demierre, 2013	F	Yes	Yes	Poorly differentiated adenocarcinoma	Stage IV	None	Caucasian	No (erlotinib)	No (pemetrexed/ cisplatin/ bevacizumab)	(23)
Prim, 2014	M	Yes	No	Invasive, acinar predominant adenocarcinoma	cT2aN3M1a (stage IV)	EGFR L858R	Caucasian	Yes (erlotinib 9 months)	Yes (14 months) (pemetrexed/ cisplatin)	(24)
Mäkinen, 2021	F	No	No	Lung adenocarcinoma	IV	EGFR L858R	Chinese	Yes (gefitinib, osimertinib)	Unknown	(15)
Ikeda, 2008	F	Unknown	Yes	3 nodules AD; 4 nodules BAC; 3 lesions AAH	T1N1M0 (stage IIA)	EGFR L858R, L861Q	East Asian	Not used	Unknown	(20)
Ohtsuka, 2011	F	Unknown	No	Lung adenocarcinoma	T4N2M1 (stage IV)	EGFR L858R	East Asian	No (gefitinib, erlotinib)	No	(21)
Demierre, 2013	F	Yes	Yes	Poorly differentiated adenocarcinoma	Stage IV	None	Caucasian	No (erlotinib)	No (pemetrexed/ cisplatin/ bevacizumab)	(23)
Prim, 2014	M	Yes	No	Invasive, acinar-predominant adenocarcinoma	cT2aN3M1a (stage IV)	EGFR L858R	Caucasian	Yes (erlotinib 9 months)	Yes (14 months) (pemetrexed/ cisplatin)	(24)
Mäkinen, 2021	F	No	No	Lung adenocarcinoma	IV	EGFR L858R	Chinese	Yes (gefitinib, osimertinib)	Unknown	(15)

Table II. Continued.

First author, year	Sex (M/F)	Smoking history	Family cancer history	Pathology	TNM stage	Secondary somatic mutation	Ethnicity	Effective for treatment		(Refs.)
								EGFR-TKI	Chemotherapy	
Ikeda, 2008	F	Unknown	Yes	3 nodules AD; 4 nodules BAC; 3 lesions AAH	T1N1M0 (stage IIA)	EGFR L858R, L861Q	East Asian	Not used	Unknown	(20)
Ohtsuka, 2011	F	Unknown	No	Lung adenocarcinoma	T4N2M1 (stage IV)	EGFR L858R	East Asian	No (gefitinib, erlotinib)	No	(21)

NA, information not available; M, male; F, female; TKI, tyrosine kinase inhibitor; AD, adenocarcinoma; BAC, bronchioloalveolar carcinoma; AAH, atypical adenomatous hyperplasia.

mutation was found in DNA derived from normal lung tissue, normal lymph node, skin and blood of the daughter, as well as a germline mutation inherited from her mother. Of note, another EGFR mutation, G719A, was discovered in the mother's carcinoma. However, as this mutation was not found in the mother's normal DNA, it was classified as a somatic mutation. Analysis from large cohorts of EGFR-mutated lung carcinomas revealed that 25% of patients with R776H/G719A-mutated tumors were classified as having mixed adenosquamous cell carcinoma, despite both the mother's and daughter's tumors being squamous cell tumors (26). This suggests that the R776H/G719A mutation may be linked to squamous cell carcinomas. Somatic codon 719 mutations have been linked to squamous carcinomas. In a recent study by Guo *et al* (27), two patients with germline EGFR R776H mutations were reported: A 42-year-old female with no smoking history and her 17-year-old son. A CT scan revealed numerous ground-glass nodes in her son's both lungs and postoperative pathology indicated the presence of adenocarcinomas. Genetic analysis of both patients revealed the same germline EGFR mutation, R776H. Her son was monitored through regular CT examination (Table III).

5. Germline mutation of EGFR P848L

The EGFR exon 21 P848L point mutation was first described by de Gunst *et al* (28) as an infrequent mutation and could silence polymorphisms. The mutation was initially identified as a germline mutation in a 31-year-old Caucasian woman who was an active smoker with a maternal grandfather diagnosed with throat cancer in 2014. The proband was resistant to erlotinib and chemotherapy (cisplatin and pemetrexed) (24). The morbidity of the P848L population is currently unclear. A large-scale retrospective study involving 31,906 Chinese patients with lung cancer found 22 germline EGFR variants in 64 patients with lung cancer, while germline EGFR P848L account for 10.9% (7/64) of the patients with EGFR germline mutation (29). A further study of 120 patients with colorectal or lung cancer reported that only one patient exhibited the P848L mutation (30).

The question arises as to whether lung cancer patients with P848L germline mutation are sensitive to EGFR-TKI. According to current research, patients with P848L germline mutation are not sensitive to EGFR-TKI (24,31). Previous studies have shown that oral erlotinib treatment in patients with the germline P848L mutation provides ~4 months of progression-free survival (24,32). However, Chinese patients with the P848L mutation alone or in combination with the L858R somatic mutation were unresponsive to EGFR-TKI, but germline P848L mutation combined with an exon 19 deletion was sensitive to gefitinib and icotinib treatment (29). Han *et al* (31) showed that patients with the P848L mutation treated with gefitinib exhibited a response similar to that of patients with wild-type EGFR, and that patients with a T790M and P848L double mutation exhibited higher resistance to gefitinib. These findings provide greater insight into the response of patients with lung cancer and rare EGFR mutations, such as the P848L mutation, to gefitinib, regardless of whether the mutation is somatic or germline. Sarcar *et al* (33) studied patients with the EGFR germline mutation and established P848L-transformed Ba/F3 cells that were resistant to multiple EGFR-TKIs but sensitive to a number of Janus kinase 1/2 inhibitors (Table IV).

Table III. Summary of patients with lung cancer exhibiting an EGFR R776H mutation.

First author, year	Sex (M/F)	Smoking history	Family cancer history	Pathology	TNM stage	Secondary somatic mutation	Ethnicity	Effective for treatment		(Refs.)
								EGFR-TKI	Chemotherapy	
van Noesel, 2013	F	No	Yes	Squamous differentiation	Unknown	Unknown	White	Unknown	Yes	(26)
van Noesel, 2013	F	No	Yes	Squamous-cell carcinoma	Unknown	EGFR G719S	White	Yes	Unknown	(26)
Guo, 2021	F	No	Yes	Lung adenocarcinoma	IA	EGFR G719A	Chinese	Unknown	Unknown	(27)
Guo, 2021	M	No	Yes	Unknown	Unknown	Unknown	Chinese	Unknown	Unknown	(27)
Lin, 2021	M	Yes	Yes	Lung adenocarcinoma	IV	EGFR T790M	Chinese	Yes (osimertinib)	Unknown	(29)
van Noesel, 2013	F	No	Yes	Squamous differentiation	Unknown	Unknown	White	Unknown	Yes	(26)
van Noesel, 2013	F	No	Yes	Squamous-cell carcinoma	Unknown	EGFR G719S	White	Yes	Unknown	(26)
Guo, 2021	F	No	Yes	Lung adenocarcinoma	IA	EGFR G719A	Chinese	Unknown	Unknown	(27)
Guo, 2021	M	No	Yes	Unknown	Unknown	Unknown	Chinese	Unknown	Unknown	(27)
Lin, 2021	M	Yes	Yes	Lung adenocarcinoma	IV	EGFR T790M	Chinese	Yes (osimertinib)	Unknown	(29)
van Noesel, 2013	F	No	Yes	Squamous differentiation	Unknown	Unknown	White	Unknown	Yes	(26)
van Noesel, 2013	F	No	Yes	Squamous-cell carcinoma	Unknown	EGFR G719S	White	Yes	Unknown	(26)

M, male; F, female; TKI, tyrosine kinase inhibitor.

Table IV. Summary of patients with lung cancer exhibiting an EGFR P848L mutation.

First author, year	Sex (M/F)	Smoking history	Family cancer history	Pathology	TNM stage	Secondary somatic mutation	Ethnicity	Effective for treatment		(Refs.)
								EGFR-TKI	Chemotherapy	
De Gunst, 2007	F	Yes	Yes	Lung adenocarcinoma	Unknown	Unknown	Caucasian	No	No	(28)
Yang, 2021	F	No	Unknown	Adenocarcinoma	Unknown	Unknown	Caucasian	Yes (gefitinib)	Unknown	(34)
Prim, 2014	F	Yes	Yes	Invasive, acinar-predominant adenocarcinoma	T4N0M1b (stage IV)	No	Caucasian	No	No	(24)
Guo, 2021	F	No	Yes	Lung adenocarcinoma	IV	L858R	Chinese	Yes (gefitinib)	Unknown	(27)
Guo, 2021	M	Yes	Yes	Lung adenocarcinoma	IV	L858R	Chinese	No	Unknown	(27)
Guo, 2021	F	No	Yes	Lung adenocarcinoma	IV	L747_T751del	Chinese	Yes (gefitinib, icotinib)	Unknown	(27)
Guo, 2021	M	Yes	No	Lung adenocarcinoma	IV	No	Chinese	Yes (icotinib, afatinib)	Unknown	(27)
De Gunst, 2007	F	Yes	Yes	Lung adenocarcinoma	Unknown	Unknown	Caucasian	No	No	(28)
Yang, 2021	F	No	Unknown	Adenocarcinoma	Unknown	Unknown	Caucasian	Yes (gefitinib)	Unknown	(34)
Prim, 2014	F	Yes	Yes	Invasive, acinar-predominant adenocarcinoma	T4N0M1b (stage IV)	No	Caucasian	No	No	(24)
Guo, 2021	F	No	Yes	Lung adenocarcinoma	IV	L858R	Chinese	Yes (gefitinib)	Unknown	(27)
Guo, 2021	M	Yes	Yes	Lung adenocarcinoma	IV	L858R	Chinese	No	Unknown	(27)

M, male; F, female; TKI, tyrosine kinase inhibitor.

6. Discussion

Germline mutations in humans contribute to both adaptive evolution and the genetic burden of the species. Various types of germline mutations have been thoroughly studied, including changes in gene dosage due to duplications or deletions ranging in size from a few base pairs to megabases, as well as changes in the number of chromosomes (34,35). While germline mutations inherited from affected or carrier parents have been linked to poor health worldwide, an increasing number of researchers are attempting to understand the mechanisms that cause diseases. The four most common EGFR germline mutations involved in lung cancer (T790M, V843I, R776X and P848L) have been described previously. Furthermore, rare germline mutations of EGFR include K757R, R831H, D1014N and L792F. Most EGFR germline mutations are generally associated with lung cancer susceptibility and the majority of these mutations are point mutations, with other mutation types being uncommon.

Nachman and Crowell (36) used an indirect measurement approach to compare human and chimpanzee data and determined that the average neutral mutation rate in the human genome is $2.3x10^{-8}$ mutations per nucleotide site per generation. Species divergence and diversity exhibit a strong relationship with the mutation rate per generation. For lung cancer, most data from western populations concluded that 3.5-8.5% of patients with lung cancer have a pathogenic germline mutation (37,38). BRCA2 and CHEK2 have been linked to an increased risk of lung cancer (39). In the Chinese population, Peng *et al* (40) reported that among 1,794 patients with lung cancer, 106 had pathogenic or likely pathogenic germline mutations, with a germline mutation-carrying rate of 5.91%. Thus, the germline mutation-carrying rate of Chinese patients with lung cancer is comparable with that of the Western population (40).

Substitution mutations, such as the lung cancer EGFR germline mutation, are genomic disorders that are likely to cause diseases and may be initiated during the early stages of testis development. A study comparing the mutational frequency of self-renewing spermatogonia (SrAp) in young and old male patients with the Apert syndrome mutation found that the fibroblast growth factor receptor 2 mutation was significantly higher (5%) in the testes of the four older donors. By contrast, two younger patients did not exhibit high mutation frequencies (41). Furthermore, not all members of the first family with the germline V843I mutation developed lung cancer. Specifically, while the proband's father and brother died of lung cancer, another brother and sister with the same germline mutation did not develop the disease (20). These observations suggest that germline mutations did not originate early during testis development. Hence, there may be selective advantages that facilitate the development of this genomic disorder. These benefits may be categorized based on sex. According to studies on Apert syndrome and achondroplasia, premeiotic testis cells carrying the causal mutation in males showed a selective advantage (42,43). In Apert syndrome and achondroplasia, the two most common mutations are 755C>G and 785C>G. Researchers found that mutant SrAp cells had an advantage over wild-type SrAp cells because they could occasionally divide symmetrically to produce two

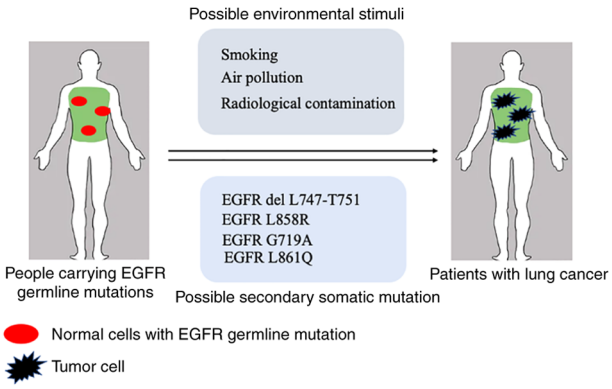

Figure 1. Schematic diagram of patients with EGFR germline mutations leading to the development of lung cancer. Individuals with EGFR germline mutation will develop lung cancer if they develop another somatic mutation (EGFR delL747-T751, EGFR L858R, EGFR G719A) or are exposed to environmental stimuli (for example, smoking, air pollution, radiological contamination). EGFR, epidermal growth factor receptor.

SrAp cells, whereas wild-type SrAp cells could only replace themselves (41,44,45). These germline selections may not be limited to nucleotide substitutions. In fragile X syndrome, for instance, trinucleotide-repeat expansion mutations could increase the frequency of germ cells with smaller alleles as testis development progresses because they have an advantage over cells with a disease allele (46-52). Aside from germline selection in males, females exhibit a higher selective advantage attributable to hereditary disease. A study reported that ovarian germline cells carrying trisomy 21 could influence the effect of maternal age on the development of Down syndrome during fetal and postnatal life (53). Based on the preceding analysis, it may be concluded that germline mutations are not passed on during birth but occur after birth. While individuals may inherit susceptibility towards developing certain familial genetic diseases at birth, the presence of these selective advantages requires confirmation through future research.

In addition to the four common types of EGFR germline mutation, some rare types of EGFR germline mutations have also been reported. Li *et al* (54) discovered the EGFR V1010M germline mutation in six individuals from four generations of family members, many of whom had lung cancer. The proband had the somatic mutation of EGFR L858R and responded to gefitinib after only 4 months. Van der Leest *et al* (55) reported the EGFR V834L germline mutation in a 57-year-old woman diagnosed with stage IIIA adenocarcinoma. While only a few cases with rare EGFR germline mutations have been reported, Lin *et al* (29) sequenced 31,906 patients with lung cancer and found 22 germline EGFR variants, including G863D, D1014N, K757R, V769M, V774M, K757R, V897A, R831H, V769M, V765M, R836C, G724S, T725M, V889M, V788M, A647T, D761Y, K754E, P753S and R776S. Patients with lung cancer and EGFR germline mutations have limited therapeutic options and new treatments should be investigated. In addition to traditional platinum-based chemotherapy, immunotherapy also has also received a lot of attention and may produce a good therapeutic effect. Trabelsi Grati *et al* (56) reported the case of a patient with metastatic NSCLC and EGFR germline and KRAS somatic mutations who exhibited a long response to immune checkpoint inhibitors. Although there is no solid

clinical evidence indicating that immunotherapy is effective in patients with EGFR germline mutations, this case report suggests that immunotherapy may be efficient in patients with lung cancer with EGFR germline mutations.

7. Conclusion

EGFR germline mutations, including T790M, V843I, R776H and P848L, have been shown to impact the development of lung cancer. The likelihood of developing lung cancer is higher for individuals with a germline mutation if they also have a somatic mutation or are exposed to environmental stimuli (Fig. 1). The efficacy of EGFR-TKI in treating patients with lung cancer with EGFR germline mutations is unclear; however, it appears to be most effective in those who have previously received EGFR-TKI treatment. Therefore, effective and appropriate treatment options should be investigated in future studies. It is recommended that individuals with germline mutations should undergo population screening as well as regular physical examinations to detect and diagnose lung tumors early.

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Authors' contributions

ML, XN designed and wrote the manuscript. JC and HL performed the literature search and drafted the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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