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Exploration of Genetic Variants Associated with Lung Cancer: A Comprehensive Review

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Abstract

Lung cancer (LC) is a widespread and prevalent disease with a high death rate. The occurrence of this terrible disease is greatly influenced by genetic, occupational and environmental risk factors. Therefore, the present review aimed to investigate and accumulate the information regarding the causative gene of lung cancer. The articles included in this study were retrieved from various online sources, including Cochrane Library, Google Scholar, EMBASE, PubMed and Web of Science databases up to October 2024. Data were extracted based on the PRISMA 2020 guidelines. The study recognized several genetic mutations that are accountable for the progression of lung cancer. The most common identified lung cancer associated with genes include *XRCC1, XRCC4, KRAS, TP53, EGFR, PI3KCA, ERCC2/XPD MET, ALK1, BRAF, HER2, LTKB-1/STK11, AKT,* and *MAP2K1*. Additionally, *HER2, MAP2K1/MEK1, AKT, NRAS* and various combinations of co-occurring mutations were also noted as stimulators of this cancer. These genes instigate lung cancer either by impairing DNA repair efficiency or interacting with various signaling pathways that result in cell proliferation, differentiation, angiogenesis, invasion and metastasis, such as, PI3k/AKT (phosphatidylinositol 3-kinase/protein kinase B) pathway, MAPKs (mitogen-activated protein) pathway, PKC (protein kinase C), JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway, as well as RAS signaling. Studying epigenetic mechanisms in lung cancer is crucial to understand the genetic variant linked to the disease and identify potential therapeutic targets and molecular targets of drugs.

Key words: Lung cancer, genetic variation, polymorphism, candidate gene.

Introduction

Lung cancer (LC) is a prevalent disease with a high mortality rate, making it a significant global factor of cancer-related mortalities (Siegel *et al.*, 2019). It is a prevalent kind of malignancy arising in the lung parenchyma or within bronchial tubes (Islam *et al.*, 2021; Gridelli *et al.*, 2015). According to GLOBOCAN (Global Cancer Observatory) report 2022, almost 2.5 million new cases diagnosed with lung cancer (12.4% of all malignancies) and 1.8 million fatalities (close to 18.7% of total cancer mortality) representing the alarming rate of this cancer globally (Bray *et al*., 2024). Recently, the rate in the developing countries is increasing theatrically as 49.9% of new cases have been detected (Bray *et al*., 2024; Moghaddam *et al*., 2024). The mortality

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was highest in Asia other than USA and Europe (Bray *et al.,* 2024). In Bangladesh, 167,256 new cases and 116,598 deaths were attributable to cancer, where lung cancer (7.8%) was the most prevalent type of carcinoma in both men and women (Ferlay *et al.,* 2024).

The overall survival rate of people with lung cancer remains low even with the availability of conventional treatments (Choong *et al.,* 2005). Only around 15% of lifelong smokers developed the cancer (Ruano-Ravina *et al.,* 2003). However, 10 -15% of this cancer in Western countries occurred in non-smokers (Couraud *et al.,* 2012). Lung cancer is influenced by various occupational and environmental risk factors, including radon, air pollution, passive smoking and importantly by genetic mutations (Ou *et al.,* 2018; Gaskin *et al.,* 2018; Hamra *et al.,* 2014; Gharibvand *et al.,* 2017). Recent research has indicated that lung cancer might also be influenced by heredity (Sato *et al.,* 2007; Meyerson *et al.,* 2004).

According to recent advances in the molecular biology of cancer, a specific genetic alteration was present in approximately 20% of squamous cell carcinomas and 60% of adenocarcinomas. These changes facilitate significant advance in personalized therapy for the treatment of lung cancer by targeting tumors with mutated genes, such as those in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma receptor tyrosine kinase (ALK) (Tan *et al.,* 2015; Peifer *et al.,* 2012). Therefore, finding the responsible genes to cause lung cancer to start and spread is a crucial part of cancer research (James *et al.,* 2023). That is why this review focused on extracting information regarding the lung cancer-associated genes, their biological function, as well as their contribution to instigating the lung cancer progression. This review will primarily concentrate on molecular genetic variants in crucial molecular targets highlighted in the literature on lung cancer includes *ERCC1, EGFR, MET, KRAS, BRAF, RET, XPD, HER2, TP53, XRCC1,* and *XRCC4.* This review will also give a new dimension in the development of precision medicine. Moreover, it will be assistive for the easier management and treatment of this cancer.

Methods and Materials

Data searching: Data related to the lung cancer and its causative gene before October 2024 was retrieved from different available online databases. Only articles published in English that met the predetermine requirements were selected from PubMed, Google Scholar, Embase, Web Sciences, and Cochrane Library. We collected data by “Cancer", “Lungs cancer/Carcinoma/ Malignancy”, “Biology of lung cancer, “Causative gene of lung cancer”, “Polymorphism/Mutation/Genetic variants” "Relationship/connection/impact/link/association/ correlation/influence”, “Treatment of lung cancer”, "Progression/development/prognostic/prognosis/progress/ growth", “Management of lung cancer” and "Survival/outcome". To find out any relevant missing articles, we checked the references of the selected articles and reviews published on this subject.

Eligibility criteria: Several criteria were considered during isolating data from the selected articles. The study excluded certain articles that did not comply the specified criteria. Studies included in the present studies were aligned with the following eligibility criteria: (a) Article on cancer, (b) Article on lungs cancer and (c) Genotypic association of lungs cancer. However, studies on animal samples, comments, editorials and articles containing insufficient data for the biology, treatment and management of lungs cancer omitted from the study.

Data extraction: The PRISMA guideline was used to extract data from the sources mentioned above (Figure 1) (Page *et al.,* 2021). Any anomalies during data collection were eliminated by a group discussion among the authors. The outcomes of the selected articles, the eligibility of the comparison study and the eligibility criteria of the present study were taken into consideration during the data extraction process.

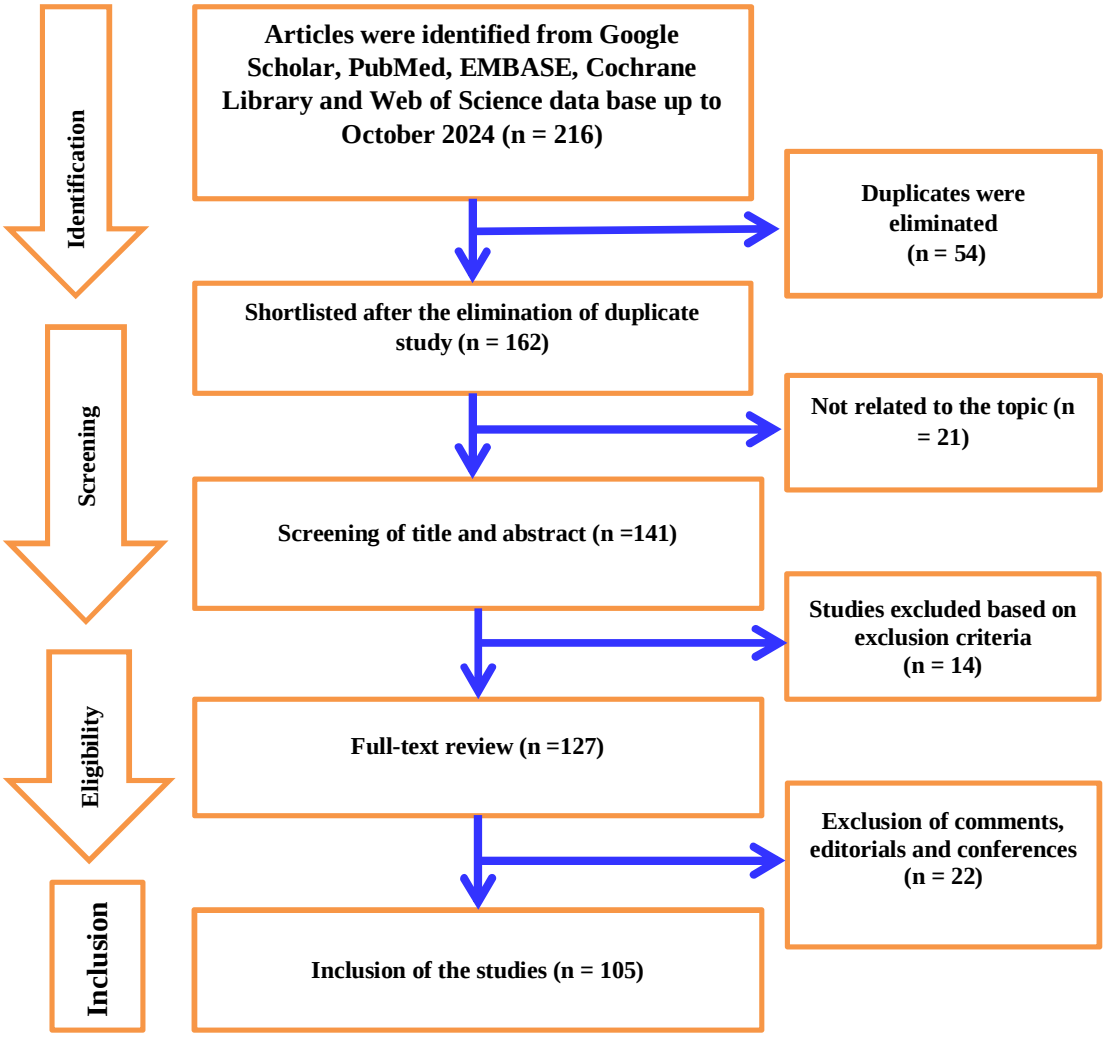

Figure 1. Data extraction as per PRISMA guideline.

Results and Discussion

Molecular genetics of lung cancer: Mutation's mechanism can be utilized to describe the tumor biology of lung cancer. It allows finding out the correlations between various mutations and the disease, particularly lung cancer. According to earlier reports, lung cancer might be caused by a number of gene mutations. *BRAF, ALK, KRAS, EGFR, MET, TP53, PI3KCA, STK11/LTKB-1, (HER2), AKT1* and *MAP2K1* are the most often found mutant genes in lung cancer (Pao and Girard, 2011; Sholl *et al.*, 2015). These alterations can be potential therapeutic targets and molecular targeting drugs such as EGFR-TKI were developed. Additionally, *ERBB2 (HER2, MAP2K1/MEK1, AKT, NRAS*) and various combinations of co-occurring mutations were noted in a few investigations (Campbell *et al.*, 2016; Leal *et al.*, 2021; Arbour *et al.*, 2018; Larsen and Minna, 2011).

The genetic pathogenesis of lung cancer is somewhat intricate and diverse (Cooper *et al.*, 2013; Kiyohara *et al.*, 2010). Certain kinds of damaged DNA are repaired by at least four different processes. The nucleotide excision repair (NER) corrects bulk lesions, base excision repair (BER) works on tiny lesions and replication mistakes are fixed by

mismatch repair. Homologous recombination (HR) and nonhomologous end-joining (NHEJ) are the two processes that make up double-strand DNA break repair (DSBR). On the other hand the HR mechanism repairs double-strand DNA breaks by aligning homologous DNA sequences and the NHEJ repair route entails the joining of the two double-strand break ends (Mohrenweiser and Jones, 1998).

Base excision repair (BER) pathway: Base excision repair (BER) is a DNA repair system that addresses minor lesions such as fragmented or non-bulky adducts, reduced or oxidized bases or those caused by methylating chemicals (Misra *et al.*, 2003). The genes that encode the three essential enzymes in this repair process are *XRCC1* (X-ray repair cross complementing group 1), *OGG1* (8-oxoguanine DNA glycosylase) and *OGG1* (Smith *et al*., 2003).

XRCC1 gene: X-ray repair cross-complementing 1 (XRCC1) is a crucial protein in BER, acting as a scaffold for POLB (polymerase-DNA directed, beta) and DNA ligase III and a single-strand break sensor through its linkage with poly (ADP-ribose) polymerase family member (Yu *et al.*, 2004; Seedhouse *et al.*, 2002; Lee *et al.*, 2002). This gene, which has 17 exons and codes for a 633 amino acid protein, is found on chromosome 19q12.2 (Kiyohara *et al*., 2010). Polymorphisms of this gene contribute to an increased risk of lung cancer by impairing DNA repair efficiency, particularly in individuals exposed to carcinogens like tobacco smoke (Hung *et al.*, 2005; Zhu *et al*., 2015). These mutations are also linked to lung cancer patients' prognosis and reactivity to platinum-based treatment (Li *et al.*, 2013). To identify lung cancer susceptibility, they could be used as molecular markers (Hanawalt, 2002).

Nucleotide excision repair (NER) system: The NER (nucleotide excision repair) system corrects several types of DNA lesions, including thymidine dimers, alkylating damage, oxidative DNA damage, bulky adducts and cross linkages. In NER, two sub pathways exist. The first is transcription-coupled DNA repair (TCR), which removes DNA damage that stops the transcribed DNA strand of active genes from continuously transcription and the second is global genome repair (GGR), which eliminates defects from the untranscribed strand of the active gene as well as from other parts of the genome (Ryu *et al.*, 2004). Genetic differences in DNA repair genes may change the host's capability to fix damaged DNA and influence the risk of cancer (Martin *et al.*, 2008). DNA repair is linked to genes *XPD* and *ERCC1*, belonging to the NER pathway and pathways for repairing double-strand breaks (Faridounnia *et al.*, 2018).

ERCC1 gene: Excision repair cross-complementing 1 (*ERCC1*) is a gene that codes for a protein of the nucleotide excision repair (NER) complex, a collection of proteins that may repair DNA damage due to UV light, electrophilic chemicals and molecules that create adducts, such as platinum (Wilson *et al.*, 2001; Benhamou and Sarasin, 2002). It is located on chromosome 19, band 19q13.32 (Lunn *et al.*, 2000). XPF endonuclease (also called ERCC4) and ERCC1 typically combine to produce heterodimeric endonuclease (XPF-ERCC1), which excises the 5′ end of DNA to the damaged spot. In addition, the XPF-ERCC1 complex takes involvement in interstream crosslink repair and homologous recombination. Functional *ERCC1* gene variants that impair DNA repair ability could therefore be a risk factor for lung malignancies brought on by tobacco use (Martin *et al*., 2008).

ERCC2/XPD gene: ERCC2/XPD (Excision repair cross-complementing group 2/ Xeroderma pigmentosum), complementation group D protein, is a key part of the NER pathway, which is essential for DNA correction. It is involved in transcription initiation, apoptosis and cell cycle control (Sameer and Nissar, 2018). The *XPD* gene, a DNA repair gene, is part of the *ERCC2* gene, which instructs the production of the XPD protein (Taylor et al., 1997). The *XPD* gene is found on chromosome 19q13.3 and has 23 exons that are approximately 54.3 kb long (Constantinescu-Aruxandei *et al.*, 2016). Both basal transcription and nucleotide excision repair of DNA damage are functions of the XPD protein. The *XPD* gene encodes a DNA helicase that unwinds DNA to

expose damaged regions. Other proteins then remove the damaged section and replace it with correct DNA. Mutations in the *XPD* gene can lead to three distinct clinical phenotypes: XP, TTD and XP with Cockayne syndrome (Wu *et al.,* 2012; Boyle *et al.,* 2008). The *XPD* gene can affect lung cancer risk and prognosis by affecting DNA repair capacity (Hsu *et al.,* 2009).

Non-homologous end-joining (NHEJ) system: This pathway is a crucial method to resolve double strand breaks (DSBs) and ensuring genome stability.

XRCC4 gene: The *XRCC4* (X-ray repair cross-complementing protein 4) gene is a protein that helps repair the breaking of DNA double-strand through this NHEJ (Yu *et al.,* 2023). It has 12 introns and 13 exons, which is found on chromosome 5q14.2. To ligate the NHEJ breaks, the XRCC4 protein combines with XLF and DNA ligase IV to create a complex (Ghaderi-Zefrehi *et al.,* 2021). Ligase IV protein levels are stabilized by XRCC4 (Liu *et al.,* 2023). This complex then creates an elastic connection between DNA ligase IV and Ku70/Ku80, directing the defective ends of DNA to unite (Zhang *et al.,* 2021). Lung cancer tissues exhibit higher levels of XRCC4 expression compared to other tissues (Hsu *et al.,* 2009). The gene is associated the risk of non-small cell lung cancer (NSCLC) and may be a new marker for research on prevention and anticancer interventions (He *et al.,* 2013; Cooper *et al.,* 2013).

Epidermal growth factor receptor (EGFR) gene: The tyrosine kinase receptor known as EGFR (epidermal growth factor receptor) belongs to the ErbB family and is aberrantly activated in a various form of epithelial cancer (Ji *et al*., 2006; Lemmon *et al*., 2014). Instructions for creating a protein that regulates cell growth and survival are provided by the *EGFR* gene (Jurišić *et al.,* 2018). It is found at location 7p11.2(70) on the chromosome 7 (Yarden and Sliwkowski, 2001). ERFR is encoded by exons 18 - 24 and is located in the short arm of chromosome 7 (7bp12). The extracellular ligand binding domain, transmembrane domain and intracellular domain make up the structural components of the EGFR receptor. EGF and TGF alpha are examples of ligands that ERFR can bind to form a heterodimer or a homodimer with another RTK. Tyrosine residues are auto-phosphorylated as a result of dimerization's stimulation of intracellular protein kinase activity. The three signal transduction pathways that cause cell proliferation, differentiation, angiogenesis, invasion and metastasis are the MAPKs, PI3k/AKT, and JAK/STAT pathways. These cascades are activated downstream as a result of this phosphorylation (Wieduwilt and Moasser, 2008; Ellison *et al.,* 2013; Brevet *et al*., 2011; Arteaga, 2002). When these pathways are mutated, normal cells multiply and proliferate uncontrollably. Three types of mutations can occur in nucleotides: Class I nucleotide mutations result from deletions in exon 19, class II from substitutions in exons 18-21 and class III from duplication or insertion of certain amino acids in 20 and 21 exons (Yarden and Sliwkowski, 2001; Wieduwilt and Moasser, 2008; Hanrahan and Solit, 2022).

BRAF gene: The *BRAF* gene, a serine/threonine-protein kinase, is a downstream effector protein of KRAS that activates the MAPK signal transduction pathway, controlling secretion, differentiation and cell division (Davies *et al*., 2002; Kazandjian *et al.,* 2024). The *BRAF* gene can be found at band 7q34 on chromosome 7 (Davies *et al*., 2002). Non-small cell lung cancer (NSCLC) is linked to BRAF mutations (Ritterhouse, L.L. and Barletta, J.A., 2015). Through the activation of the MAPK (ERK1/2, MEK1/2) pathway, this mutation inhibits death of cell and promotes cell growth and proliferation (Brose et al., 2002; Davies *et al*., 2002). In lung cancer, *BRAF* mutations are frequently linked to a poorer prognosis and resistance to conventional chemo therapies (Davies *et al*., 2002). They are critical drivers of tumorigenesis in lung cancer, making them important targets for precision medicine approaches (Wan *et al*., 2004). Targeted therapy that combines BRAF and MEK inhibitors can effectively cure BRAF-mutant non-small cell lung cancer, improving patient outcomes (Jančík *et al.,* 2010).

KRAS gene: Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene produces KRAS

protein, is essential signal transducer that controls a number of biological reactions during cell division, proliferation and survival is the KRAS protein (Cox *et al.,* 2014). The KRAS protein is crucial in controlling the MAPK as well as PI3K/AKT pathways by influencing the rate at which both healthy and malignant cells proliferate (Prior *et al.,* 2012). It participates in cell signaling pathways and belongs to the RAS family, which also includes NRAS and HRAS (Cox *et al.,* 2014). Under typical circumstances, KRAS attaches to GTP, hydrolyzes it to GDP and then phosphorylates it. Following the conversion of GTP to GDP, KRAS is turning off. HRAS and NRAS control this on/off switch. The additional signaling pathway that drives cellular growth is triggered by this event. KRAS's hyper active state, when GTP is firmly coupled to KRAS, allows for unchecked proliferation (Bamford et al., 2004). KRAS is the most common oncogenic gene driver in human malignancies and the most frequently mutated member of the RAS family (Laghi *et al.,* 2002). The majority of lung adenocarcinomas have *KRAS* mutations (Wennerberg *et al.,* 2005; Prior *et al.,* 2012). The transforming potential of RAS proteins is achieved through a gene mutation that replaces an amino acid at positions 12, 13 or 61. Due to these alterations, RAS signaling is constitutively activated in types of RAS with reduced GTPase activity (Kempf *et al.,* 2016; Shigematsu and Gazdar, 2006). G12A, G12V, G12C and G12D mutations are the most prevalent KRAS mutations found in smokers, males and Western countries, while G12C is the most prevalent mutation among smokers (Adderley *et al.,* 2019; Cheng, 2024; Raghav and Moasser, 2023).

HER2 gene: Human epidermal growth factor receptor 2 (HER2), a key EGFR family transmembrane glycoprotein, is crucial for cell proliferation, differentiation and survival (Moasser, 2007; Ferguson, 2008). The *HER2* gene, sometimes called *ErbB2,* is a recognized proto-oncogene found on chromosome 17's long arm (17q21). It is made up of a transmembrane domain, an extracellular area, and a tyrosine kinase domain with a C-terminal regulatory region. Since HER2 lacks a recognized soluble ligand, dimerization with other ligand-bound HER family members initiate downstream signaling. Additionally, HER2 can stay activated on the cell membrane for a longer period of time and is less likely to internalize and degrade. The most prevalent modifications in NSCLC are HER2 mutation, HER2 amplification and HER2 overexpression. These alterations are known to mediate the carcinogenic process in a range of solid tumors. The activation of various signaling pathways, including MAK, PI3K/AKT, PKC and STAT leads to unchecked cell proliferation (Guimaraes and Hainaut, 2002; Williams and Schumacher, 2016).

TP53 (Tumor Protein p53) gene: The *TP53* (Tumor protein p53) which is a tumor suppressor gene involved in essential cellular functions like DNA repair, apoptosis, senescence, transcription, genomic stability and cell cycle regulation. *TP53,* located on chromosome 17p13, is a 53 kD nuclear phosphoprotein with 11 exons spanning 20 kilobases (Harris, 1996). It halts the cell cycle when DNA damage is detected, enabling the repair mechanism to function (Cooper *et al.,* 2013). It is often rendered inactive in most human malignancies due to structural changes, interactions with viral products, and endogenous cellular processes (Mogi and Kuwano, 2011). About 65% of non-small cell lung cancers and 90% of small cell carcinomas exhibit TP53 inactivation (Husgafvel-Pursiainen *et al.,* 2000). Smokers and nonsmokers have different TP53 mutational spectra (Velculescu and El-Deiry, 1996). In NSCLC, abnormal p53 has been identified as a poor prognostic factor. Additionally, treatment resistance is associated with genetic alterations in TP53 (Gallo *et al.,* 2024; Heydt *et al.,* 2023).

MET gene: The gene MET (mesenchymal epithelial transition) is expressed on the surface of epithelial cells by RTK (Crepaldi *et al.,* 2024). The *MET* gene is located on chromosome 7 at the q21-31 locus (Drilon *et al.,* 2017). Under normal conditions, MET consists of a tyrosine kinase domain, transmembrane domain, extracellular domain, and transmembrane unit with four IPT domains, SEMA and PSI. The HGF/c-MET with

other pathways, including JAK/STAT, Ras/MAPK, and PI3K/AKT are activated by this entire process (Heydt *et al.*, 2023). The MET proto-oncogene causes numerous cancers and mutations in this gene promote the proliferation, invasion, metastasis and angiogenesis of tumor cells (Zhang *et al.*, 2018). MET signaling abnormalities can lead to lung cancer tumorigenesis through *MET* gene amplification, mutation, rearrangement and overexpression (Wang *et al.*, 2010). Additionally, mutations caused MET/HGF protein overexpression results in acquired resistance to ERFR-TKIs (Cai *et al.*, 2024; de Groot *et al*., 2006), which is linked to a poor prognosis for non-small cell lung cancer (NSCLC) (Kohno *et al.*, 2015).

RET gene: The *RET* (Rearranged during Transfection) gene encodes RET receptor, expressed in neural crest-derived cell lineages and crucial for regulating cell proliferation, differentiation, migration and survival during embryogenesis (Kohno *et al.*, 2012). It is found in chromosome 10 (10q11.2). Its translocation can produce a variety of fusion proteins (Takeuchi *et al.*, 2012). In NSCLC, the most prevalent RET fusion accounting for 1-2 percent of cases, is KIF5B-RET. The *RET* gene is overexpressed as a result of this fusion. Younger, nonsmoking individuals are typically affected (Choudhury and Drilon, 2020). There are currently over 50 different forms of RET rearrangement identified in NSCLC patients. Chromosome rearrangement is the primary mechanism by which abnormal structural activation is accomplished (Luo *et al.*, 2013). The most frequent RET rearrangements in NSCLC are pericentric or paracentric inversion, of which kinesin family member 5B (KIF5B) accounts for approximately 68.3%; NCOA4 for 1.2%; CCDC6 for 16.8%; and the uncommon fusions TRIM33-RET, EPHA5-RET and CLIP1-RET (Li *et. al.*, 2023).

Epigenetic alterations

DNA methylation: One common epigenetic change associated with lung cancer is aberrant DNA methylation. Hypermethylation in the promoter regions of tumor suppressor genes like *CDKN2A*, *RASSF1A*, and *P16* silences these genes and contributes to tumor development. The use of methylation patterns as biomarkers for prognosis, treatment outcomes and early detection is growing (Belinsky 2005).

Histone modifications: Alterations in histone modification enzymes are frequently seen in tumors, and these changes can impact the expression of important genes involved in tumorigenesis and treatment resistance. Changes in histone modifications, such as acetylation and methylation, impact gene expression patterns and contribute to the progression of lung cancer (Yang *et al.*, 2022).

Inherited genetic factors: Certain inherited genetic mutations increase susceptibility to lung cancer, particularly mutations in DNA repair genes and cell cycle regulators. For instances:

BRCA1/2 mutations: Lung cancer susceptibility is also increased by *BRCA1/2* mutations, which are more frequently linked to ovarian and breast cancer. These mutations cause genomic instability and the emergence of cancer by impairing DNA repair mechanisms. Patients with *BRCA* mutations may benefit from treatments like platinum-based chemotherapy that focus on DNA repair mechanisms ((Del Giglio *et al.*, 2023).

CHEK2 Mutations: Mutations in the gene CHEK2, which regulates the cell cycle and repairs DNA, have been associated with a higher risk of lung cancer and other cancers. Mutations in *CHEK2* disrupt the DNA damage checkpoint mechanism, resulting in genomic instability ((Zhang *et al.*, 2022).

Conclusion

Innate biological factors and environmental factors interact to cause lung cancer. Crucially, the development of this disease is significantly influenced by genetic variation. Numerous early genetic studies identified several genes, including *XRCC1, XRCC4, ERCC2/XPD, KRAS, EGFR, TP53, PI3KCA, MET, BRAF, ALK1, HER2, STK11/LTKB1, AKT1* and *MAP2K1*, as being linked to lung cancer. Furthermore, it was observed that this cancer was stimulated by *HER2, MAP2K1/MEK1, AKT, NRAS*

and different combinations of co-occurring mutations. By reducing the efficiency of DNA repair or interfering with different signaling pathways that cause abnormal cell proliferation and differentiation, angiogenesis, invasion and metastasis, these genes cause lung cancer. The identification of genetic alterations in lung cancer not only improves the understanding of the disease but also holds significant implications for prognosis and therapeutic strategies, i.e. prognosis, personalized medicine, biomarkers for early detection and so on.

Abbreviations

ALK1, Activin Receptor Like Kinase 1; ALT1, alanine transaminase; BER, Base excision repair; BRAF, B-Raf proto-oncogene; BRCA, Breast cancer gene; CDKN2A, Cyclin-dependent kinase inhibitor 2A; CHEK2, Checkpoint kinase 2; DSBR, double-strand DNA break repair; ERCC2, Excision repair cross-complementing group-2; EGFR, epidermal growth factor receptor; GTP, guanosine triphosphate; GDP, Gemcitabine, dexamethasone, and cisplatin; GGR, global genome repair; HER2, Human epidermal growth factor receptor 2; HR, Homologous recombination; HRAS, Harvey Rat sarcoma virus; KRAS, Kirsten rat sarcoma viral oncogene homolog; PKC, Protein kinase C; MAPK, mitogen-activated protein kinase; MET, mesenchymal epithelial transition; NER, nucleotide excision repair; NHEJ, Non-homologous end-joining; NSCLC, non-small cell lung cancer; P16, Cyclin-dependent kinase inhibitor protein; PSI, Precision Surgical Interventions; RAS, Rat sarcoma; RASSF1A, Ras association domain family 1, isoform A; RET, Rearranged during Transfection; RTK, Receptor tyrosine kinases; STAT, signal transducer and activator of transcription; STK11, Serine/threonine kinase 11; TCR, transcription-coupled DNA repair; TP53, Tumor protein p53; XPD, Xeroderma pigmentosum complementation group-D; XRCC1, X-ray repair cross-complementing-1; XRCC4, X-ray repair cross-complementing-4.

Conflict of interest

Authors have no conflict of interest.

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