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Genetics of Lung Cancer -Disease Causing and Risk Factors

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Abstract—*Lung cancer is the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total). Cancer is now known as a disease of genomic alterations. It is becoming more accepted now that the identification of genomic alterations in lung cancer can impact therapeutics, especially when the alterations represent "oncogenic drivers" in the processes of tumorigenesis and progression. Mutations in fourteen genes causing the disease were investigated. Chromosome location of the change, normal function and the function after mutation were investigated. Commonly identified genetic/genomic alterations were missense or nonsense mutations, small insertions or deletions, alternative splicing, and chromosomal fusion rearrangements. It was enquired how mutation in these genes leads to dysfunctional protein and how other mutations may have no effect at all. Mutational analysis of AKT1, ALK, BRAF, DDR2, EGFR, ERBB2, KRAS, MAP2K1, NRAS, PIK3CA, PTEN and RET genes revealed how a single change in the gene can lead to enhanced or constitutive cell signaling, increased survival, invasiveness, and tumorigenicity.*

1. INTRODUCTION

Lung cancer has been the most common cancer in the World for several decades. Given that tobacco smoking is the leading risk factor for lung cancer, it stands to reason that lung cancer in those that abstain from tobacco use would have additional novel risk factors which might include genetics or environmental exposures. Some of the main non-tobacco exposures associated with lung cancer are household air pollution, radon, occupational exposures, and outdoor air pollution. There are two main groups of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Most people with lung cancer have NSCLC. The signs and symptoms of lung cancer can take years to develop and they may not appear until the disease is advanced. Symptoms of lung cancer that are in the chest: Coughing, Pain in the chest, shoulder, or back unrelated to pain from coughing, change in colour or volume of sputum, shortness of breath, rrecurrent lung problems, such as bronchitis or pneumonia. A mutation in one DNA nucleotide (SNP, single-nucleotide polymorphism) may cause the formation of a wrong amino acid and the resulting proteins may or may be over expressed or not functional at all. Also mutations in genes lead to the production of a protein that is constantly turned on (constitutively activated) **Figure.1**. As a result, cells are signaled to constantly proliferate, leading to tumor formation. When these gene changes occur in cells in the lung, lung cancer develops [1]. In addition to genetic changes, researchers have identified many personal and environmental factors that expose individuals to cancer-causing compounds (carcinogens) and increase the rate at which somatic mutations occur, contributing to a person's risk of developing lung cancer. The greatest risk factor is long-term tobacco smoking, which increases a person's risk of developing lung cancer 20-fold. Other risk factors include exposure to air pollution, radon, asbestos, or second hand smoke; long-term use of hormone replacement therapy for menopause; and a history of lung disease such as tuberculosis, emphysema, or chronic bronchitis.

2. METHODOLOGY

Genetics Home Reference (GHR), a national library of medicine's website for consumer information about genetic conditions was used. Pathogenic and non-pathogenic genes related to Lung cancer were noted [2]. NCBI Gene and SNP Tutorial, resource for knowing the gene sequences; gene alleles; mutations; amino acid sequences for proteins was used. The chromosome location; normal function of pathogenic and non-pathogenic genes causing Lung cancer; family name and the altered functions of the genes after mutation were investigated and recorded in the form of a table. SNP database of the National Center for Biotechnology Information, U.S. National Library of Medicine was used for extracting the rsID of the alleles of interest. Variation and phenotype, i.e., whether the mutant variant is autosomal recessive or dominant; clinical significance and effect of the mutated genes on the amino acid sequence was recorded in the form **Table.1** and **Table 2**.

3. RESULTS

Table 1: Gene Family, Location, Normal Function and Function after Mutation of genes

GENES	LOCATION	NORMAL FUNCTION IN CELL	FUNCTION AFTER MUTATION
AKT1	long (q) arm of chromosome 14 at position 32.33	Oncogenic in nature. Produces protein AKT1 kinase that performs functions as cell growth, division, differentiation, cell survival and controls apoptosis. It is essential for development and function of nervous system.	Mutant AKT1-E17K has been reported to promote anchorage-dependent and independent proliferation, increases the ability to migrate and invade through reconstituted basal membrane as well as to survive and duplicate in stress conditions *in vitro*, leading to the emergence of a cell population endowed with the capability to form aggressive, undifferentiated tumours at high efficiency.
ALK	short (p) arm of chromosome 2 between positions 23.2 and 23.1	Produces protein anaplastic lymphoma kinase which performs process of transduction and cellular processes. It regulates early proliferation of nerve cells.	R1275Q mutation falls within the kinase activation loop in a region strongly associated with activating mutations in many different protein kinases, such as *BRAF*.
BRAF	long (q) arm of chromosome 7 at position 34	Oncogenic in nature. Produces protein that transmits outside signals into the cell's nucleus. It regulates proliferation, differentiation, migration, and apoptosis and is essential for normal development before birth.	Mutations results in inactivation of BRAF. Mutants cannot phosphorylate MEK, activate CRAF, or stimulate cell signaling. Therefore, appear catalytically and biologically inactive.
DDR2	long (q) arm of chromosome 1at position 23.3	Functions in regulation of cell growth ,differentiation and metabolism.it is required for normal bone development regulating osteoblast differentiation and chondrocyte maturation and regulates remodeling of extracellular matrix .	Mutation occurs in the kinase domain. Cell lines harboring *DDR2* mutations appear to be dependent upon mutant kinase activity for growth and survival.
EGFR	short (p) arm of chromosome 7 at position 11.2	Produces protein called epidermal growth factor receptor that when bound to a ligand signals the cell and promote cell growth, proliferation and cell survival.	When mutated the receptor protein is constantly turned on even if it is not bound to ligand and thus cell constantly proliferate and survive leading to tumor formation. When these changes occur in the lungs, lung cancer develops.
ERBB2	long (q) arm of chromosome 17 at position 12	Encodes protein of epidermal growth factor family.	The exon 20 insertion results in increased ERBB2 activity and enhanced signaling through downstream pathways, resulting in increased survival, invasiveness, and tumorigenicity.
KRAS	short (p) arm of chromosome 12 at position 12.1	Oncogenic in nature. Produces protein K-Ras which functions primarily in regulating cell division. It transmits outside signals to cell nucleus and these signals thus instruct cell to grow and mature. It changes GTP molecule to GDP.	Due to change in amino acid glycine at position 12 or 13 in the K-Ras protein it becomes constantly turned on and direct cell to grow and divide in an uncontrolled way leading to tumor formation.
MAP2K1	long (q) arm of chromosome 15 at position 22.31	Produces protein MEK1 which transmits the outside signal to the cell nucleus and functions in growth and development before and after the death, transcriptional regulation, migration and apoptosis.	This mutation occurs outside of the kinase domain of MEK1. Preclinical data have shown that this mutation leads to increased MEK1 kinase activity in vitro and constitutive activation of the MAPK signaling pathway.
NRAS	short (p) arm of chromosome 1 at position 13.2	Oncogenic in nature. Forms a protein N-Ras which transmit outside signal to cell nucleus and these signal .It converts GTP to GDP.	Due to mutation, the growth pathway cannot be turned off. This can cause cells to grow out of control and lead to cancer..

PIK3CA	long (q) arm of chromosome 3 at position 26.32	Functions in cellular activities such as migration ,proliferation ,production of new proteins, regulation of several hormones and maturation of fat cells	Mutant PIK3CA proteins have increased catalytic activity resulting in enhanced downstream signaling and oncogenic transformation
PTEN	long (q) arm of chromosome 10 at position 23.31	Produces enzyme which is tumor suppressor and functions as phosphatases, performs apoptosis and is involved in angiogenesis and maintains stability of cell's genetic information	Mutated PTEN cannot stop PI3K from turning on AKT1. So, AKT1 is on more than it should be in these cells. This could cause cells to grow out of control and lead to cancer
RET	long (q) arm of chromosome 10 at position 11.21	Produces protein essential for normal development of nerve cells and controls involuntary body function such as heart beat and is also needed in spermatogenesis and normal kidney development.	Mutations alter the correct folding of RET thereby interfering with RET maturation, intracellular trafficking or stable expression on the cell surface.
RIT1	long (q) arm of chromosome 1 at position 22	Belongs to class oncogenes. Produces a protein that helps cell survive during period of cellular stress. It converts GTP into GDP and transmits outside signals to cell nucleus. Functions in cell division, differentiation, and apoptosis.	Cysteine mutations may alter the correct folding of RET thereby interfering with RET maturation, intracellular trafficking or stable expression on the cell surface

Table 2: From DNA to Amino acid (only some of the data is presented)

GENE	VARIATION	CLINICAL SIGNIFICANCE	rsID	EFFECT ON AMINO ACID
AKT1	c.73C>T (p.Arg25Cys)	Pathogenic	rs397514644	Positively charged to polar uncharged
AKT1	c.49G>A (p.Glu17Lys)	Pathogenic	rs121434592	Negatively charged to positively charged
ALK	c.3824G>A (p.Arg1275Gln)	Pathogenic	rs113994087	Positively charged to polar uncharged
ALK	c.3575G>C (p.Arg1192Pro)	Pathogenic	rs113994089	Positively charged to polar uncharged
BRAF	c.1781A>T (p.Asp594Val)	Pathogenic	rs121913338	Negatively charged to non polar
BRAF	c.1040G>C (p.Arg347Pro)	Uncertain significance	rs397516884	Positively charged to polar uncharged
DDR2	c.2304T>A (p. Ser768Arg)	Pathogenic	rs397516965	Polar uncharged to positively charged
DDR2	c.2254C>T (p.Arg752Cys)	Pathogenic	rs121964863	Positively charged to polar uncharged
EGFR	c.2155G>A (p.Gly719Ser)	Pathogenic	rs28929495	Non polar to polar uncharged
EGFR	c.2155G>C (p.Gly719Arg)	Pathogenic	rs28929495	Non polar to positively charged
EGFR	c.2155G>T (p.Gly719Cys)	Pathogenic	rs28929495	Non polar to polar uncharged
EGFR	c.2156G>A (p.Gly719Asp)	Pathogenic	rs121913428	Non polar to negatively charged
EGFR	c.2464G>A (p.Ala822Thr)	Uncertain significance	rs397517125	Non polar to polar uncharged
EGFR	c.2419C>T (p.Arg831Cys)	Uncertain significance	rs371228501	Positively charged to polar uncharged
ERBB2	c.2236G>A (p.Gly746Ser)	Pathogenic	rs28933369	Non polar to polar uncharged
ERBB2	c.2650G>A (p.Glu884Lys)	Pathogenic	rs28933368	Negatively charged to positively charged
ERBB2	c.2616G>C (p.Gln872His)	Uncertain significance	rs193920750	Polar uncharged to positively charged
KRAS	c.183A>C (p.Gln61His)	Pathogenic	rs17851045	Polar uncharged to positively charged
KRAS	c.182A>T (p.Gln61Leu)	Pathogenic	rs121913240	Polar uncharged to non polar
KRAS	c.182A>G (p.Gln61Arg)	Pathogenic	rs121913240	Polar uncharged to positively charged
KRAS	c.181C>G (p.Gln61Glu)	Pathogenic	rs121913238	Polar uncharged to negatively charged
KRAS	c.181C>A (p.Gln61Lys)	Pathogenic	rs121913238	Polar uncharged to positively charged
KRAS	c.38G>A (p.Gly13Asp)	Pathogenic	rs112445441	Non polar to negatively charged
KRAS	c.37G>T (p.Gly13Cys)	Pathogenic	rs121913535	Non polar to polar uncharged
KRAS	c.37G>C (p.Gly13Arg)	Pathogenic	rs121913535	Non polar to positively charged
KRAS	c.37G>A (p.Gly13Ser)	Pathogenic	rs121913535	Non polar to polar uncharged
KRAS	c.35G>A (p.Gly12Asp)	Pathogenic	rs121913529	Non polar to negatively charged
KRAS	c.436G>A (p.Ala146Thr)	Uncertain significance	rs121913527	Non polar to polar uncharged
KRAS	c.76A>T (p.Asn26Tyr)	Uncertain significance	rs794727277	Polar uncharged to aromatic
MAP2K1	c.167A>C (p.Glu56Pro)	Pathogenic	rs121908794	Polar uncharged to polar uncharged
MAP2K1	c.171G>T(p.Lys57Asn)	Pathogenic	rs869025608	Positively charged to polar uncharged

MAP2K1	c.199G>A (p.Asp67Asn)	Pathogenic	rs727504317	Negatively charged to polar uncharged
MAP2K1	c.412G>A (p.Glu138Lys)	Uncertain significance	rs730880504	Negatively charged to positively charged
NRAS	c.182A>T (p.Gln61Leu)	Pathogenic	rs11554290	Polar uncharged to non polar
NRAS	c.182A>G (p.Gln61Arg)	Pathogenic	rs11554290	Polar uncharged to positively charged
NRAS	c.181C>G (p.Gln61Glu)	Pathogenic	rs121913254	Polar uncharged to negatively charged
NRAS	c.181C>A (p.Gln61Lys)	Pathogenic	rs121913254	Polar uncharged to positively charged
NRAS	c.179G>A (p.Gly60Glu)	Pathogenic	rs267606920	Non polar to negatively charged
NRAS	c.38G>A (p.Gly13Asp)	Pathogenic	rs121434596	Non polar to negatively charged
NRAS	c.37G>T (p.Gly13Cys)	Pathogenic	rs121434595	Non polar to polar uncharged
NRAS	c.37G>C (p.Gly13Arg)	Pathogenic	rs121434595	Non polar to positively charged
NRAS	c.37G>A (p.Gly13Ser)	Pathogenic	rs121434595	Non polar to polar uncharged
NRAS	c.35G>A(p.Gly12Asp)	Pathogenic	rs121913237	Non polar to negatively charged
NRAS	c.34G>T (p.Gly12Cys)	Pathogenic	rs121913237	Non polar to polar uncharged
NRAS	c.34G>C (p.Gly12Arg)	Pathogenic	rs121913237	Non polar to positively charged
NRAS	c.34G>A (p.Gly12Ser)	Pathogenic	rs121913250	Non polar to polar uncharged
PIK3CA	c.1624G>A (p.Glu542Lys)	Pathogenic	rs121913273	Negatively charged to positively charged
PIK3CA	c.1633G>A (p.Glu545Lys)	Pathogenic	rs104886003	Negatively charged to positively charged
PIK3CA	c.1634A>C (p.Glu545Ala)	Pathogenic	rs121913274	Negatively charged to non polar
PIK3CA	c3140A>T(p.His1047Leu)	Pathogenic	rs397517452	Positively charged to non polar
PIK3CA	c.1252G>A (p.Glu418Lys)	Uncertain significance	rs397517199	Negatively charged to positively charged
PTEN	c.55G>A (p.Asp19Asn)	Pathogenic	rs121909233	Negatively charged to polar uncharged
PTEN	c.70G>A (p.Asp24Asn)	Pathogenic	rs786201995	Negatively charged to polar uncharged
PTEN	c.70G>C (p.Asp24His)	Pathogenic	rs786201995	Negatively charged to positively charged
PTEN	c.70G>T (p.Asp24Tyr)	Pathogenic	rs786201995	Negatively charged to aromatic
PTEN	c.71A>G (p.Asp24Gly)	Pathogenic	rs797044910	Negatively charged to non polar
PTEN	c.79T>A (p.Tyr27Asn)	Pathogenic	rs746128825	Aromatic to polar uncharged
RET	c.1825T>C (p.Cys609Arg)	Pathogenic	rs77558292	Polar uncharged to positively charged
RET	c.1825T>G (p.Cys609Gly)	Pathogenic	rs77558292	Polar uncharged to non polar
RET	c.1826G>A (p.Cys609Tyr)	Pathogenic	rs77939446	Polar uncharged to aromatic
RET	c.1826G>T (p.Cys609Phe)	Pathogenic	rs77939446	Polar uncharged to aromatic
RET	c.1831T>C (p.Cys611Arg)	Pathogenic	rs377767391	Polar uncharged to positively charged
RET	c.1831T>G (p.Cys611Gly)	Pathogenic	rs377767391	Polar uncharged to non polar
RET	c.1832G>A (p.Cys611Tyr)	Pathogenic	rs377767397	Polar uncharged to aromatic
RET	c.1832G>T (p.Cys611Phe)	Pathogenic	rs377767397	Polar uncharged to aromatic
RET	c.1833C>G (p.Cys611Trp)	Pathogenic	rs80069458	Polar uncharged to aromatic
RET	c.1852T>C (p.Cys618Arg)	Pathogenic	rs76262710	Polar uncharged to positively charged
RET	c.1852T>G (p.Cys618Gly)	Pathogenic	rs76262710	Polar uncharged to non polar
RET	c.1854C>G (p.Cys618Trp)	Pathogenic	rs377767400	Polar uncharged to aromatic
RET	c.1858T>C (p.Cys620Arg)	Pathogenic	rs77316810	Polar uncharged to positively charged
RET	c.1858T>G (p.Cys620Gly)	Pathogenic	rs77316810	Polar uncharged to non polar
RET	c.509C>T (p.Thr170Ile)	Uncertain significance	rs200547906	Polar uncharged to non polar
RET	c.95C>T (p.Ser32Leu)	Risk factor	rs76764689	Polar uncharged to non polar
RET	c.191C>T (p.Pro64Leu)	Risk factor	rs77596424	Polar uncharged to non polar
RET	c.406G>A (p.Glu136Lys)	Risk factor	rs79014735	Negatively charged to positively charged

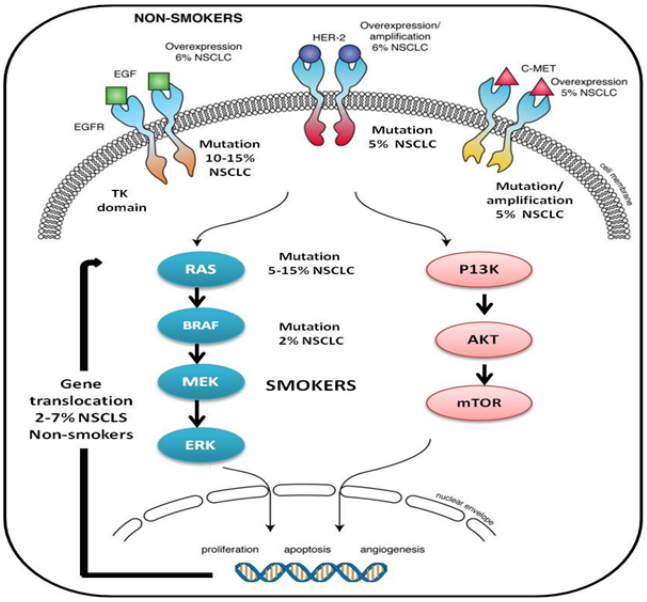

Fig. 1: EGFR pathway in NSCLC **Discussion**

There are 14 genes responsible for lung cancer: AKT1, ALK, BRAF, DDR2, EGFR, ERBB2, KRAS, MAP2K1, NRAS, PIK3CA, PTEN, RET, RIT1 and ROS1**.** Some of these have been studied.

AKT1: AKT1 gene provides instructions for making a protein called AKT1 kinase and plays a critical role in many signaling pathways. AKT1 kinase also helps control apoptosis. Signaling involving AKT1 kinase appears to be essential for the normal development and function of the nervous system. In Glu17Lys mutation AKT1 gene is always turned on. This can cause cells to grow out of control and lead to cancer. Mutant AKT1- Glu17Lys has been reported to promote anchorage-dependent and -independent proliferation, increases the ability to migrate and invade through reconstituted basal membrane as well as to survive and duplicate in stress conditions *in vitro*, leading to the emergence of a cell population endowed with the capability to form aggressive, undifferentiated tumors at high efficiency. Also, Arg25Cys mutation can be of clinical significance since Argnine is a positive-charged, polar amino acid, whereas Cysteine is a small hydrophobic amino acid: the Arg25Cys variation is therefore a nonconservative change [3].

ALK: ALK gene provides instructions for making a protein called anaplastic lymphoma kinase, part of a family of proteins called receptor tyrosine kinases (RTKs). Receptor tyrosine kinases transmit signals from the cell surface into the cell through a process called signal transduction. These signaling pathways are important in many cellular processes such as cell growth and division or differentiation. Three mutations in the tyrosine kinase domain of ALK (Gly1128Ala, Arg1192Pro and Arg1275Gln) were studied. The Arg1275Gln mutation falls within the kinase activation loop in a region strongly associated with activating mutations in many different protein kinases, such as *BRAF*. This amino acid substitution results in an electropositive residue being replaced by a more electronegative one, possibly mimicking activating phosphorylation events. The Arg1192Pro mutation occurred at the beginning of the β4 strand of the kinase domain, and although it is predicted to be driver mutations with high confidence the mechanism for activation is not yet clears [4].

BRAF: BRAF gene provides instructions for making a protein that helps transmit chemical signals from outside the cell to the cell's nucleus. This protein is part of a signaling pathway known as the RAS/MAPK pathway, which controls several important cell functions like cell growth and division, differentiation, migration, and apoptosis. The most common Gly466Val mutation is in the part of BRAF that passes along the cell growth signal. In cells with this mutation, BRAF can no longer pass along the signal. Cancer may develop in cells that have both the BRAF G466V mutation and another mutation that keep the pathway on. Mutations at Asp594Gly result in inactivation of BRAF. The carboxy oxygen of this highly conserved residue (the "D" of the DFG motif) plays a critical role in chelating Mg^{2+} and stabilizing ATP binding in the catalytic site. As in other kinases, mutation of this residue causes inactivation and thus cancer mutants appear inactive.

DDR2: Discoidin domain receptor tyrosine kinase 2; Receptor tyrosine kinases (RTKs) play a key role in the communication of cells with their microenvironment. These molecules are involved in the regulation of cell growth, differentiation, and metabolism. RTKs have a tripartite structure with extracellular, transmembrane, and cytoplasmic regions. The Ser768Arg occurs in the kinase domain.Cell lines harboring *DDR2* mutations appear to be dependent upon mutant kinase activity for growth and survival [6].

EGFR: EGFR gene provides instructions for making a receptor protein called the epidermal growth factor receptor, which spans the cell membrane so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. The binding of a ligand to an epidermal growth factor receptor allows the receptor to attach to a nearby receptor protein (dimerize), turning on (activating) the receptor complex. As a result, signaling pathways within the cell are triggered that promote cell growth and division and survival. The Gly719Cys mutation occurs within exon 18, which encodes part of the kinase domain. Several additional independent mutations have also been described at position 719: Gly719Ala, Gly719Asp, Gly719Ser, and Gly719Val. Collectively, these point mutations occur with a frequency of approximately 2-3% in EGFR-mutated lung tumors) [7, 8].

ERBB2: This gene encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. This protein has no ligand binding domain of its own and therefore cannot bind growth factors. However, it does

bind tightly to other ligand-bound EGF receptor family members to form a heterodimer, stabilizing ligand binding and enhancing kinase-mediated activation of downstream signalling pathways. The ERBB2 gene has 27 exons. Exon 20 makes amino acids 770-831. Most exon 20 insertions occur between amino acids 775 and 781. These mutations are in the part of ERBB2 that is inside the cell. When the inside part is on, ERBB2 can turn on other proteins. In most cells with these mutations, the signal is not needed. The inside part of ERBB2 is always on. The exon 20 insertion results in increased ERBB2 activity and enhanced signaling through downstream pathways, resulting in increased survival, invasiveness, and tumorigenicity [9].

KRAS: KRAS gene provides instructions for making a protein called K-Ras that is involved primarily in regulating cell division. As part of a signaling pathway known as the RAS/MAPK pathway, the protein relays signals from outside the cell to the cell's nucleus. These signals instruct the cell to grow and divide or to mature and take on specialized functions (differentiate). Tobacco components, particularly benzo[a]pyrene, are believed to be strong carcinogens for *KRAS* mutated lung cancer. The most common mutations in KRAS occur at positions 12 (Gly12Asp), 13 (Gly13Asp, and 61(Glu61Arg, Glu61Leu). All three of these amino acid positions are important in turning on the protein. When a mutation occurs at any one of these positions, the growth pathway cannot be turned off. The result of these mutations is constitutive activation of *KRAS* signaling pathways [10].

MAP2K1: The MAP2K1 gene provides instructions for making a protein known as MEK1 protein kinase. This protein is part of a signaling pathway called the RAS/MAPK pathway, involved in controlling the proliferation, differentiation, migration, and apoptosis. The Gln56Pro, Asp67Asn and Lys57Asn mutations occurs in the part of MAP2K1 that controls if the protein is on or off. In cells with this mutation, MAP2K1 can always turn on ERK and cause cells to grow out of control and may lead to cancer. This mutation occurs outside of the kinase domain of MEK1 [11].

NRAS: The NRAS gene provides instructions for making a protein called N-Ras that is involved primarily in regulating cell division. The N-Ras protein is a GTPase and acts like a switch, and it is turned on and off by the GTP and GDP molecules and play important roles in cell division, cell differentiation, and the self-destruction. More than 50% of *NRAS* mutations involve A:T >T:A transversions). Carcinogens known to induce A:T >T:A transversions include 7,12-dimethylbenz[a]anthracene (DMBA), which is released into the environment through the combustion of fossil fuels. Perhaps the combination of smoking and such a carcinogen are associated with the etiology of *NRAS* mutated lung cancer. The most common mutations in NRAS occur at positions 12, 13, and 61. All three of these amino acid positions are important in turning on the protein. When a mutation occurs at any one of these positions, the growth pathway cannot be turned off. This can cause cells to grow out of control and lead to cancer [12].

PIK3CA: The PIK3CA gene provides instructions for making the p110 alpha (p110α) protein, which is one piece (subunit) of an enzyme called phosphatidylinositol 3-kinase (PI3K). The p110α protein is called the catalytic subunit because it performs the action of PI3K, while the other subunit (produced by a different gene) regulates the enzyme's activity. PI3K signaling is important for many cell activities, including cell growth and division (proliferation), movement (migration) of cells, production of new proteins, transport of materials within cells, and cell survival. Three most frequently observed PI3-kinase mutations: Glu542Lys, Glu545Lys, and His1047Leu. Mutations in the helical domain of p110α (Glu542Lys and Glu545Lys) also confer enhanced enzymatic activity. His1047Leu mutation results in an amino acid substitution at position 1047 in PIK3CA, from a Histidine to a Leucine. This mutation occurs within the highly conserved kinase domain. Mutant PIK3CA proteins have increased catalytic activity resulting in enhanced downstream signaling and oncogenic transformation in vitro [13].

PTEN: PTEN gene provides instructions for making an enzyme that is found in almost all tissues in the body. and acts as a tumor suppressor. The PTEN enzyme modifies other proteins and fats (lipids) by removing phosphate groups, each of which consists of three oxygen atoms and one phosphorus atom. PTEN enzyme is part of a chemical pathway that signals cells to stop dividing and triggers cells to self-destruct through a process called apoptosis. PTEN prevent uncontrolled cell growth that can lead to the formation of tumors. This could cause cells to grow out of control and lead to cancer [14].

RET: The RET gene provides instructions for producing a protein that is involved in signaling within cells. The RET protein spans the cell membrane, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning of the protein allows it to interact with specific factors outside the cell and to receive signals that help the cell respond to its environment. When molecules that stimulate growth and development (growth factors) attach to the RET protein, a complex cascade of chemical reactions inside the cell is triggered. These reactions instruct the cell to undergo certain changes, such as dividing or maturing to take on specialized functions. Cysteine 609, 611, 618 or 620 mutations may alter the correct folding of RET thereby interfering with RET maturation, intracellular trafficking or stable expression on the cell surface [15].

4. CONCLUSION

Twelve pathogenic genes were found responsible for lung cancer. Most prominent ones include AKT1, ALK, BRAF, DDR2, EGFR, ERBB2, KRAS, MAP2K1, NRAS, PIK3CA, PTEN and RET. These mutations promote anchorage-dependent and independent proliferation; increase the ability to migrate and invade through basal membrane. Many

mutations effect the phosphorylation and therefore lead to enhanced or constitutive cell signaling resulting in increased survival, invasiveness, and tumorigenicity. The mutations result in substitution of amino acids from charged to uncharged; uncharged to charged or even negatively to positively charged. Such changes in charge and polarity of residues can have drastic consequences as an enzyme becomes dysfunctional. Apart from the pathogenic genes, non-pathogenic genes were also noted. Some gene mutations are silent, having no effect at all. Changes in these genes are of uncertain significance or some of them are only considered as 'risk factor' for example Arg972Gly in case of RET gene. These genes can be employed as significant markers for early detection and treatment of lung cancer. It is estimated that around 10-20 genetic events including alterations in oncogenes and tumor suppressor genes (TSG) will have been occurred by the time a lung tumor becomes clinically evident. These alterations if studied and characterized systematically with present day advanced molecular analytic techniques can be developed as potential predictive and prognostic markers. Moreover, by understanding molecular mechanisms of the disease and potential treatment, molecularly targeted treatment strategies can be adopted.

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