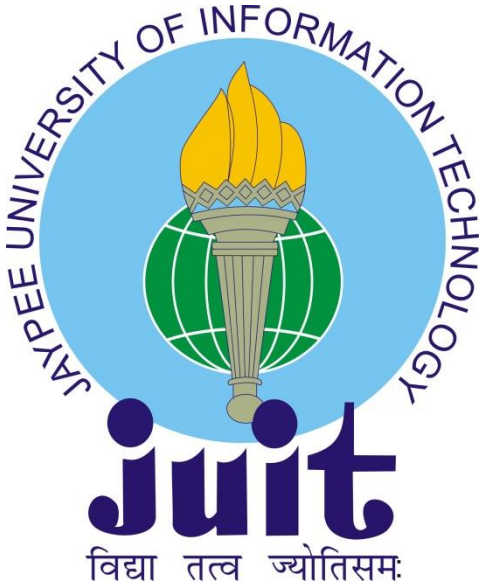
FDFT1 VARIANT rs2645424 AND CANCER SUSCEPTIBILITY IN HIMACHAL PRADESH POPULATION

Project report submitted in partial fulfillment of the requirement for the Degree of

Bachelor of Technology in Biotechnology

Submitted by

Isha Srivastava (151811)



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METADATA

Title	**FDFT1 Variant rs2645424 and Cancer Susceptibility in Himachal Pradesh population.**
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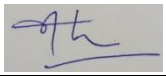
CERTIFICATE

This is to certify that the work titled "**FDFT1 Variant rs2645424 and Cancer Susceptibility in Himachal Pradesh Population**", submitted by Isha Srivastava in partial fulfilment for the award of degree of Bachelor of Technology in Biotechnology of Jaypee University of Information Technology, Waknaghat has been carried out under my supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of this or any other degree or diploma.



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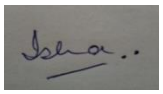
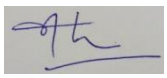
SUMMARY

Cancer is one of the main cause of death all around the world and the most recent information expresses that around 18 million individuals have disease and out of them around 2 million bites the dust each year. In spite of the fact that number of studies have been performed and a great deal are as yet going on so as to discover the underlying driver of a cell to get destructive and cause this dangerous disease in the body and unquestionably lead to passing and to discover better alternatives for the treatment of the cancer cell growth. Among the different elements behind the growth of cancerous cells, there are natural elements, hereditary components and way of life factors. In any case, discovering the genetic factors can be a significant achievement in finding the pattern of development of cancer.

Here in this study, we have been studying the pattern of single nucleotide polymorphism rs2645424 of Farnesyl-diphosphate Farnesyl-transferase1 (FDFT1) gene among the Himachal Pradesh population so as to find out its relationship with the susceptibility towards common cancers.





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[1] INTRODUCTION

When the cell starts growing uncontrollably or in an abnormal way, and moves beyond their boundaries and starts to invade the neighbouring parts of the body, spreading to other organs, a condition commonly called as 'Cancer' arises. It is the most dreadful disease of 20th century. Cancer has been spreading continuously and its incidence has increased in the twenty-first century. This condition is becoming highly frightening such that now every 4th person is prone to a life-time cancer risk [1-3]. The word cancer was coined by a great physician from Greece, "Hippocrates- Father of Medicine". He made use of the phrase "Carcinos" to describe a tumor formed from non-ulcers and "Carcinoma" to describe such tumors [4]. As we are aware that there is a natural cell cycle and lifespan of a normal cell in the body, in which every cell experiences a decline or death phase (cell death is known as Apoptosis), tumorous cells lack this ability and continues to grow and multiply rapidly. This rapid increase in the quantity of cells is the characterization feature of cancer. This condition arises due to mutation of the genes that controls the cell division cycle, due to which unregulated and uncontrolled cell division occurs. There are times when cells divide continuously and start piling on each other giving rise to malignant tumors which gives rise to cancer, and sometimes when there is no uncontrolled division, then tumors are either called Benign and Premalignant tumors [5]. Cancer can start developing at any part of the body and even spread from one part to the other parts [6]. In 2018, about 9.6 million deaths occurred due to cancer, which was the second largest cause of deaths globally. Around 18 million cases of cancers are registered in the world of which 9.5 million cases are male patients and 8.5million are female patients [7,8]. Today, cancer is becoming the second most common causes of deaths after the cardiovascular diseases [8]. Over 2.2 million people are surviving from cancer in our country [10]. Annually about 11, 57,294 lakh are registered cases with 7, 84,821 deaths among which 9.81% (4, 13,519) are males and 9.42% (3, 71,302) are females. Oral cancer and lung cancer represent over 25% of deaths in males and oral and breast cell malignant cell growth represent 25% tumors in females [10, 11].

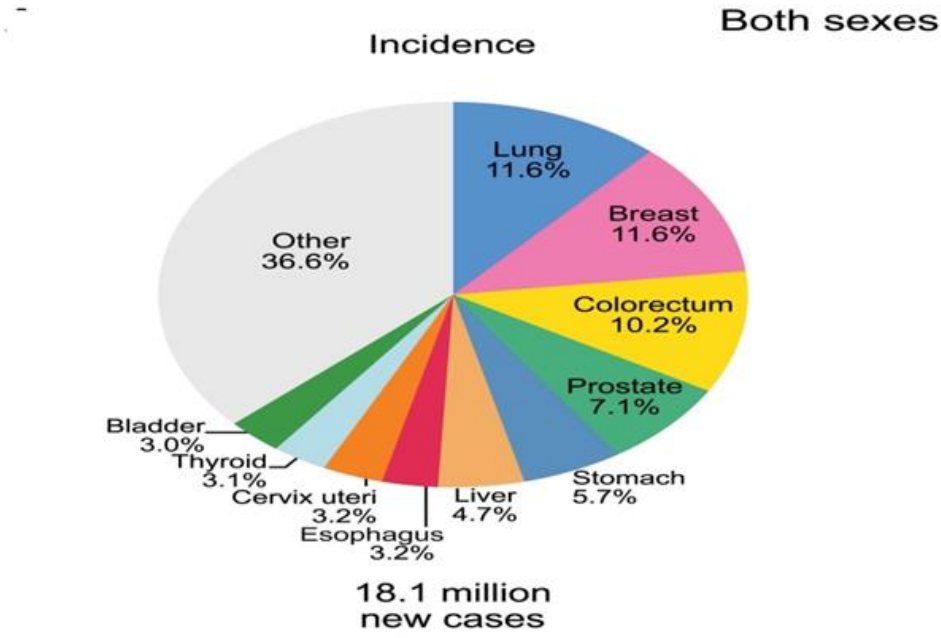

FIGURE 1: The distribution of cases of 10 most common cancers in 2018 for both sexes [9]

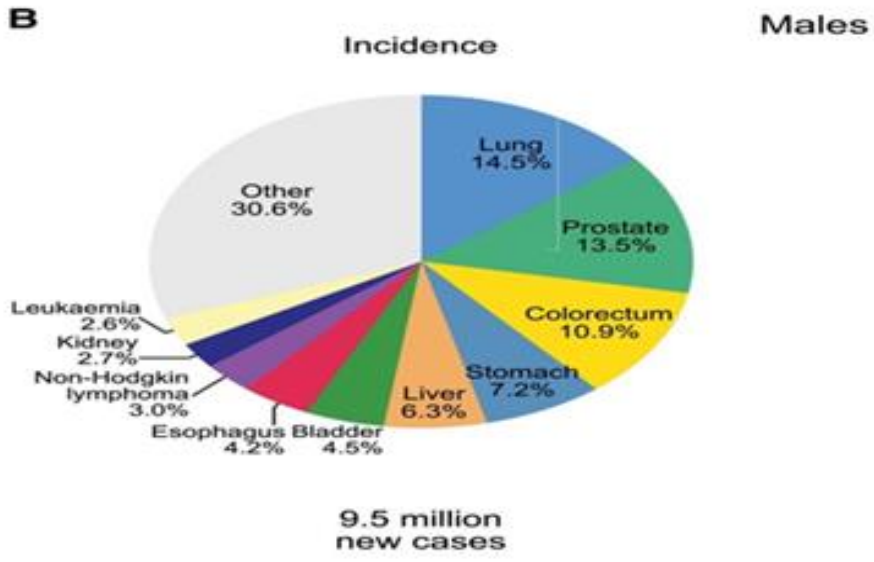

FIGURE 2: The distribution of cases of 10 most common cancers in 2018 for males [9].

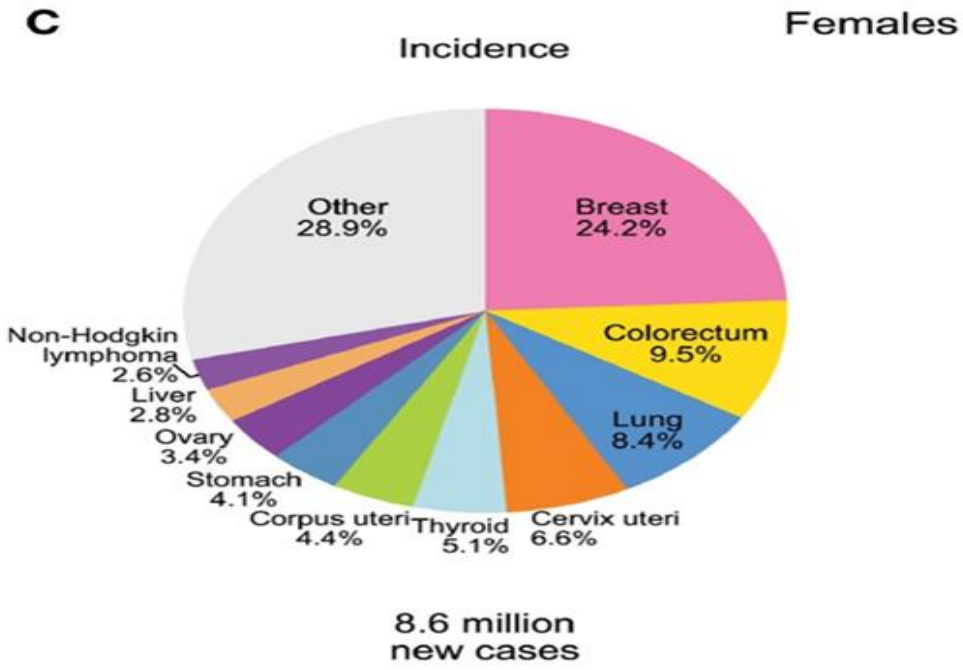

FIGURE 3: The distribution of cases of 10 most common cancers in 2018 for females [9]

CAUSES OF CANCER:

Cancer is mainly caused by mutation in the somatic body cells during the lifespan of an individual, but sometimes, rarely, it might be inherited. It is even possible that both of these factors played a role in giving rise to cancer. Genes that are involved in an initiation of cancer formation are of two kinds:

- The oncogenes,
- The Tumor suppressor genes.

Mutation of a Proto-oncogene results in the formation of oncogenes which becomes overactive and starts producing more proteins. Tumor suppressor genes lose protective control over cells and become non functional leading to cancer, resulting in the initiation of carcinogenesis causing Cancer [13].

More than one type of mutation is possible, from missense mutation in which amino acid is altered, to frame-shift mutation in which reading frame is altered, or non-sense mutation in which truncation of protein product takes place. Even though this is not essential that only mutation in amino acids cause the initiation of carcinogenesis, sometime the effects of mutations at splicing and promoter sites also results to this condition. There can be a number of mechanisms that may cause mutations like deletion of small DNA segments or deletion of large DNA segments, Inversions, Translocations, and so on. These mutations can happen for a variety of reasons like due to some DNA and RNA viruses, Ultraviolet radiations, Ionizing radiations, chemicals , cigarette smoking, chimney soot, food preservatives and many other – these are known as Carcinogenic substances, which can cause disease in the various manners:

- By straightforwardly harming the DNA in cells prompting transformations (upsetting the ordinary procedure of cell cycle)

- By not influencing the DNA directly, however rather making cells divide at a quicker rate than typical, that can increase the odds that DNA changes and transformations will happen. [13-15].

When the cancer genetics is discussed, there are certain factors of risks that results in cancer such as transfer from the parents or grandparents to the next generation. It has been reported that out of every 10 cancer cases, there is 1 case which is related with the hereditary influence, but as a matter of fact cancer can't be caused by just inheriting it from previous generation. It is possible that the genes inherited to the family members have a cancer gene in it but to activate or trigger it will require something from outside, such as some sort of mutation. It is also possible that the member of the family who inherited the cancer gene may not develop cancer, and while someone else from the family who didn't inherit the cancer gene may develop [16]. Hereditary cancers can be identified early on initial stages of development due to similar kinds of symptoms of cancer as other family member had from whom cancer is inherited [16]. Till today, more then 30-types of this sort of cancer taking place of hereditary were discovered to be mutant in heterozygous situations [17].

So as to discover the key parts of the inherited components for malignant growth we can take a look at the protein coding locale solely from the genome to distinguish the variety in expression. The non-protein coding location of the genome fills in as a layout for the translation of different non-coding RNAs. There are two kinds of RNA non coding areas: small non-coding RNA and the long non coding RNA (LncRNA). LncRNAs are found in antisense or sense direction to protein coding region of the genome and can work in cis (major) and trans too. It incorporates a broadened methods of systems by which the LncRNAs impact during the time spent carcinogenesis be that as it may, the examinations show that their significant job is to direct the site of particularity to the chromatin modifying buildings to cause changes at epigenetic levels [18-19].

The misexpression of LncRNAs have lead to the advancement of malignancies and enter in to carcinogenesis. There are significantly 5 kinds of approaches by which the lncRNA can influence in progressiveness of the malignant growth:

(a) by chromatin rebuilding,
(b) by transcriptional co-actuation and restraint,
(c) protein restraint,
(d) post transcriptional alterations and
(e) contending formicroRNA by official with the PTEN quality [20].

FDFT1 gene and its role in cancer:

An important structural component of lipid rafts is cholesterol, which can be involved in pathways like growth of cell, its survival, and other features required for cancer cells. These processes can be increased by addition of cholesterol or by synthesizing it in a metabolic pathway that FDFT1 enzyme controls. The mevalonate pathway is one of the major metabolic pathways that utilize acetyl-CoA to create sterols and isoprenoids. The level of this catalyst in varied kinds of human cancer has been examined to play a vital role in carcinogenesis and conjointly in behaviour of cancer [21].

This study is designed to investigate the role of variant rs2645424 present in Farnesyl-diphosphate Farnesyl-transferase1 (FDFT1) gene in the susceptibility of Himachal Pradesh population towards common cancer types.

[2] REVIEW OF LITERATURE

[2.1] CANCER

The formation of abnormal cells that undergoes uncontrollable division of cells and spreads to other organs as well is termed as Cancer. It is known that human cells grow, and then divide to form newer cells, and in case the cells are old, they die which are then replaced with newer cells. In case the cells are further divided to create new cells but fails to die resulting in the survival of old cells as well, then the formation of tumor takes place [22,23].

There usually are two kinds of tumor: Benign and Malignant.

Benign tumors: Benign tumors are non cancerous in nature; they do not grow into other body areas and are usually curable. When benign Tumor occurs in brain then it can be dangerous as it may crowd the space of skull. As there is a possibility that they may start metastasizing and develop into cancer, they are removed through surgeries. Benign tumors do not recur if once they are removed. Examples of Benign tumors are:

- Adenomas develop in glandular epithelial tissue, which occurs in a layer that covers organs and different structures in the body.
- Fibroids, or fibromas, are a kind of tumors that can develop on the stringy or connective tissue of any organ.
- Haemangioma are tumors that structure when veins develop unnecessarily.
- Lipomas are a type of delicate tissue tumor and comprise of fat cells. They can show up at any age [24].

Malignant tumors: Malignant tumors are cancer causing as they are made up of cancerous cells and can be spread to other organs and tissues within one's body. They possess properties of metastasis. Spread to other body parts takes place via lymph nodes, blood, vessels, and cause cancer. Types of Malignant tumors are:

- Carcinoma: These tumors structure from epithelial cells, which are available in the skin and the tissue that spreads or lines the body's organs.
- Sarcoma: These tumors start in connective tissue, for example, ligament, bones, fat, and nerves.
- Germ cell tumor: These tumors create in the cells that produce sperm and eggs.
- Blastoma: These tumors structure from early stage tissue or creating cells [24, 25].

[2.2] TYPES OF CANCER

There exist more than 100 kinds of cancers and these can be classified in various ways based on the area it is present, the organ it affects, or the different tissues in which it originates, however the doctors has differentiated cancers among four different groups: Carcinoma, Sarcoma, Leukemia, Lymphoma.

(a) Carcinomas: Contribute about 85% of cancers. This type of cancer is related to epithelial cells. Breast cancer, brain cancer, cervical cancer, skin cancers are all included in this.

(b) Sarcomas: Related to connective tissue of mesodermal origin. Cartilage cancer, Bone cancer and Muscle cancer are all included in this.

(c) Lymphomas: Contribute about 5% of cancers. Lymphocytes, Lymph nodes, spleen cancers are included in this type.

(d) Leukaemia: Caused by the rise in number of WBC [26]**.**

(1) CARCINOMA:

It is the cancer of epithelial tissue, the tissue that is present underneath the skin. It starts in the cells that make up the skin or organs which are having tissue lining like liver and kidneys. They are able to divide uncontrollably but they don't always spreads to other body parts and stays in those cells or tissues where it started.

Carcinomas can be further sub-divided into the following:

(a) **Adenocarcinoma:** This is a kind of carcinoma that begins in cells called "glandular cells." These cells make bodily fluid and different liquids. The glandular cells are found in various organs in your body [27].

(b) **Basal cell carcinoma**: This is the most widely recognized type all things considered. It happens in cells covering the most profound part of the skin's external layer. Basal cell carcinomas frequently resemble:

- Open wounds
- Red patches
- Pink developments
- Sparkly knocks or scars [27]

(c) **Ductal carcinoma in-situ**: This is where malignant cells are found inside the ducts of the breast. But in DCIS, the disease has not completely formed or spread into close zones. About all the ladies who were found to have this cancer were cured from this disease [27].

(d) **Invasive ductal carcinoma**: This sort of breast cancer begins in a milk pipe however spreads into the greasy tissue of the bosom. It can spread to different part of the body through the lymph framework and circulation system [27].

(e) **Renal cell carcinoma**: The most widely recognized kind of kidney cancer. It normally develops as a solitary tumor inside the kidney [27].

(f) **Squamous cell carcinoma**: This sort of carcinoma frequently appears on the skin, but can likewise be found in different parts of the body. For example, cells lining, areas that are exposed to the sun. Squamous cell carcinomas can include:

- Layered red patches
- Open injuries
- Development with a downturn in the center
- Moles [27,28]

2. SARCOMA:

Sarcomas are cancer of the cells that connect and support other tissues in our body-connective tissue. Sarcoma usually forms in the bones, muscles, cartilages, nerves, fats, blood vessels of legs and arms. There exist more than fifty types of carcinoma which when narrowed down to 2 main kinds:

- **Soft Tissue Sarcoma:** Most sarcomas forms in the muscles, veins or other delicate tissues of the body, and are known as soft tissue sarcomas. They can be found in any piece of the body. The vast majority of them start in the arms or legs. They can likewise be found in the storage compartment, head and neck region, inside organs, and the zone toward the rear of the stomach (belly) cavity.

- **Bone Sarcoma:** Fewer sarcomas forms in the bone, and are known as bone malignant growths or bone sarcomas. It happens when the cells that develop new bone structure a dangerous tumor. It's the most well-known sort of bone malignant growth in youngsters and adolescents. It can influence grown-ups, as well. In any case, young men are well on the way to get it. A blunder in your DNA, or your hereditary code, causes osteosarcoma. Bone-developing cells commit tumors by error [29].

3. LYMPHOMA:

Lymphoma develops is lymphocytes, which are a type of WBC hence it is a cancer of Lymphatic system. Due to the region where it is present, it is very easy for Lymphoma to spread to different organs and tissues of the body. Mostly it spreads to the lungs, liver, or bone marrow **[30].**

4. LEUKEMIA:

It is the cancer of White Blood Cells (WBC). Leukaemia is also known as blood cancer. In this WBC crowds the RBC and the platelets. Leukaemia develops due to the trouble of blood cell production. It can be differentiated among two parts as per the severeness level of the disease and the disease time period termed as Chronic and Acute.

1. **CHRONIC LEUKEMIA:**
   Chronic leukemia grows gradually, and the early indications might be gentle and go unnoticed. Constant leukemia is most generally analyzed after a standard blood test. The indications might be dubious and could happen because of numerous other ailments.
   The signs of this cancer may include:

- General sentiments of discomfort, for example, sleepiness, bone and joint torment, or brevity of breath
- Weight reduction
- Lost hunger
- A fever
- Night sweats
- Anemia

2. **ACUTE LEUKEMIA:**

   Acute leukemia grows rapidly. The dividing mechanism of defective cells is quick.
   The basic signs of this cancer are:

- Low white platelet tallies,
- Infections,
- Sleepiness that doesn't leave with rest,
- Brevity of breath ,
- Pale skin ,
- Perspiring around evening time,
- A slight fever ,
- Wounding without any problem,
- Bone and joint throbs ,
- Slow recuperating of cuts,
- Little red dabs under the skin [31].

[2.3] CAUSES OF CANCER:

Cancer is not caused by a single factor. There are many factors that form cancer. Carcinogens are the name that is given to the substances that causes cancer.

Carcinogen can be a chemical like tobacco smoke; can be environmental agent; viral agents; biological factors or can be inherited genetic factors. So, these factors can be categorized into the following groups**:**

(a) Life-style related factors: Factors like cigarette smoking, fried foods, red meat, exposure to sun, alcohol, infections, stress, and obesity are all included in lifestyle related factors. Mostly 25-30% of deaths related to cancer are because of tobacco and 30-35% is due to diet**.**

(b) Biological factors: These are body related factors consisting of immunity, age of the person, sex of the person etc. For a major part of life, our immune framework effectively battles malignant cells, executing them as they created. That is its activity; the main employment is Natural Killer cells that destroys cancer cells and infections. For cancer to create, our immune framework should be exhausted, insufficient, incapable to slaughter malignant growth cells as quick as they form very fast.

(c) Environmental factors: Such factors which could contribute to be of primary factors which results in cancer, like pollution, exposure to radiations, UV or Randon or to other fine particulate matter. It has been studied that, 80-90% of malignant tumors are caused by external environmental carcinogens [35].

(d) Viral agents: There are many viral agents that are responsible for producing cancer like HBV, HCV, and HPV. Durable diseases with high-chance HPVs can cause malignant growth in parts of the body where HPV taints cells, for example, in the cervix, oropharynx (the piece of the throat at the rear of the mouth, including the delicate sense of taste, the base of the tongue, and the tonsils), rear-end, rectum, penis, vagina, and vulva. HPV infects the squamous cells lining of the internal surfaces of the mentioned organs. This leads to the squamous cell carcinoma. Cervical malignancies originating from HPV infection in the cervix and are called adenocarcinomas.

Other factors which contribute to the factors which could be the causative cancer agents could be Radiation. Ionizing exposure (soil radon, X-ray) and non-ionizing factors (UV radiation from sun) might result in cancer. When breathed in, these radioactive particles can harm the cells that line the lung. Long haul introduction to radon can prompt lung malignant growth, the main disease demonstrated to be related with breathing in radon.. Cancer can also be formed by over-intake of some medicines like Antineoplastic that causes deficiency in immune system **[32-34]**.

We are going to review here about 2 varying kinds of cancers found among the Himachal Pradesh Population:

(a) Lung Cancer.

(b) **Head and neck cancer**.

[2.4] <u>LUNG CANCER</u>:

An uncontrolled and rapid division and growth of cells of lungs that are usually derived from epithelial cells is termed as lung Cancer. This uncontrollable division and the rapid growth of the cells leads to metastasis by invasion into neighbouring cells, tissues and organs and spread to other regions as well, apart from lungs. In case of males, it is most frequent cause of cancer death, whereas in case of females, it is the second most common after breast cancer [39,40]. Lung cancer is primarily associated with cigarette smoking, but can be developed in non-smokers as well. Roughly about 25% cases of lung cancer are seen in non-smokers. Sometimes having a parent or a grandparent who was affected with cancer raises the cancer risk in lungs as it can be inherited too. There were many other known risk factors associated with lung cancer in non-smokers such as radon exposure, job-related exposure to certain carcinogens, air-pollution, burning coal indoor, infections by HPV, second-hand smoking or passive smoking [38,39,40].

Lung cancer can be differentiated into two primary types:

(a) Small cell lung cancer,

(b) Non-small cell lung cancer.

- **Small cell lung cancer:** such lung carcinoma which is formed in the lung tissues. SCLC contributes about only 15% of all the lung cancers. Further Small cell lung cancer are differentiating into 2 types:

(a) **Oat Cell cancer also known as Small cell carcinoma**: It is profoundly dangerous and could spread rapidly to different pieces of the body, Oat cell carcinoma is less common.

(b) **Combined small cell carcinoma**: Combined SCLC (CSCLC) is an uncommon subtype of SCLC, characterized by the blend of SCLC and NSCLC parts. [41,42] .

- **Non-small cell lung cancer:** NSCLC contributes up to 85% of total lung cancers. Such kind is the most common type pf cancer having multiple features. Different type of NSCLC has different type of cancer cells as they grow and extend in different ways. NSCLC is further divided into:

(a) **Adenocarcinoma:** This type of NSCLC starts in the cells that would ordinarily emit substances, for example, mucus. This sort of lung disease happens basically in current or previous smokers, yet it is likewise the most widely recognized kind of lung malignancy seen in non-smokers. Adenocarcinoma is normally found in the external pieces of the lung and is bound to be found before it has spread,

(b) **Large cell carcinoma:** Also known as Undifferentiated carcinoma, it can show up in any piece of the lung. It will in general develop and spread rapidly, which can make it harder to treat,

(c) **Squamous cell carcinoma:** Start in squamous cells, which are level cells that line within the aviation routes in the lungs. They are regularly connected to a past filled with smoking and will in general be found in the focal piece of the lungs, close to a primary aviation route [43 ,44, 45].

- **Causes of lung cancer:**

There are a number of factors that can make a person vulnerable to lung cancer such as lifestyle, genetic, environmental, age, exposure to radon, pollution, occupational interaction to carcinogens, gender, race, and lung disease etc. [46]. Some common factors are:

(a) Smoking:

Smoking is the major cause of lung cancer. It increases lung cancer risk by 5 to 10 times. Even in non-smokers the risk increases by about 20% if they are exposed to any kind of environmental tobacco i.e. passive smoking. 73 carcinogens are known to be present in a cigarette smoke. In the year 2000, around 90% lung cancer deaths across the developed world in men were due to smoking [46, 47].

(b) Radon:

It is a radioactive gas that occurs naturally and damages tissue by releasing alpha particles. After smoking, radon is the major cause of lung cancer with almost 21,000 deaths due to lung cancer [48, 49].

(c) Family history:

People with lung cancer family history are known to be at a 50% more risk of lung cancer and may be influenced by both environmental and lifestyle factors of the individual [50].

(d) Genetics:

It is known that polymorphism on 5, 6 and 15 chromosomes affect and increase in the lung cancer risk. SNPs encoding for the qualities, for example, CHRNA5, CHRNA3 and CHRNB4 alongside RGS17 are some which have expanded relationship of lung malignancy chance
Few lung malignancies are connected to genes. Oncogenes are a kind of gene that assists cells with developing and divide. Tumor suppressor genes prevent cells from partitioning or make them vanish when you needn't bother with them any longer. changes in these qualities permit cells to gap and gap until they structure tumors. Most gene changes that raise lung disease chance occur during an individual's lifetime. Once in a while, somebody acquires these transformations from their folks. Genes are bound to cause a few sorts of lung disease than others. [51].

Diagnosis of Lung Cancer:

The carcinoma diagnosing on uncertain patients can be done by an entire staging work up which incorporates analysis of metastasis; can be done by diagnosis of tissues; also, by functional evaluation of a patient [52].

Staging of lung cancer:

Staging is important as it helps us distinguish it into groups telling us about particular treatments that will be appropriate. Differentiating staging on the basis of clinical terms:

Occult stage: Also known as hidden stage. The mucus contains a very small amount of cancer cells but it is not visible in any scans and biopsy.

Stage 0: Tumor has started developing on the upper layer only but hasn't yet spread out as size of the tumor is very small in size.

Stage 1: Tumor has reached lungs but has not spread to any other part yet.

Stage 2: The disease has started spreading to lymph nodes and areas around the lungs.

Stage 3: Cancer has reached further deep into the lymph nodes and also to other parts.

Stage 4: Cancer already spread to other body parts which maybe be brain, liver, or bones [53- 55].

Treatment:

Targeted therapy, chemotherapy, radiation therapy, and surgery are the major treatment options for lung cancer [56]:

(a) Surgery: It is mostly applicable to the early stage cancer and at that stage it is considered the best healing option [57].

(b) Chemotherapy: It is a before surgery procedure when the lung cancer has reached advanced stages [58].

(c) Radiation therapy: It plays a major role when followed by chemotherapy. It provides very less serious toxicity as well a nice rate of control on the disease [59].

(d) Targeted therapy: This therapy focuses on targeting those proteins that controls the division, growth and the spread of lung cancer [60].

Preventions that can be taken to avoid lung cancer: Prevention is better than cure so the things that can be done for reducing the lung cancer risk are:

(a) Stop smoking: Tobacco smoking is as yet the main source of lung malignancy and is the principle reason that this illness goes into metastasis so effectively and spread to different pieces of the body. So if an individual hasn't smoke ever he ought not smoke at all and the ones who do it ought to leave it as quickly as time permits. Passive smoking is likewise a main explanation of the lung disease, since

numerous examinations have demonstrated that latent smoking is more deadly than the dynamic ones, Since it has long term impacts and is increasingly risky for the youngsters in developing ages as in long term it may prompt conduct and mental changes.

(b) Avoid radon exposure: By testing for this gas.

(c) Avoid coming in contact with carcinogens: Take legitimate consideration and defensive measures while working in a condition where cancer-causing agents are there and follow all the wellbeing measures and directions like wearing covers, gloves, washing hands when eating, and so forth.

(d) By staying healthy: Probably the most ideal approaches to maintain a strategic distance from an illness can be taking a decent also, nutritious eating regimen that can help keep up the invulnerability of the body. Regular admission of good nutrients and cancer prevention agents can help in annihilating the unsafe cancer-causing agents from the body protecting you from improvement of any sort of contamination.

(e) By exercising regularly: One of the best and effective approach to remain solid can be by doing physical exercise each day. One must perform enough measure of activity in any terms such as playing, yoga, cross-fit, running and so on. These aides in detoxifying the body of the cancer-causing agents and produce great insusceptibility in the body and maintaining a strategic distance from such hurtful diseases.

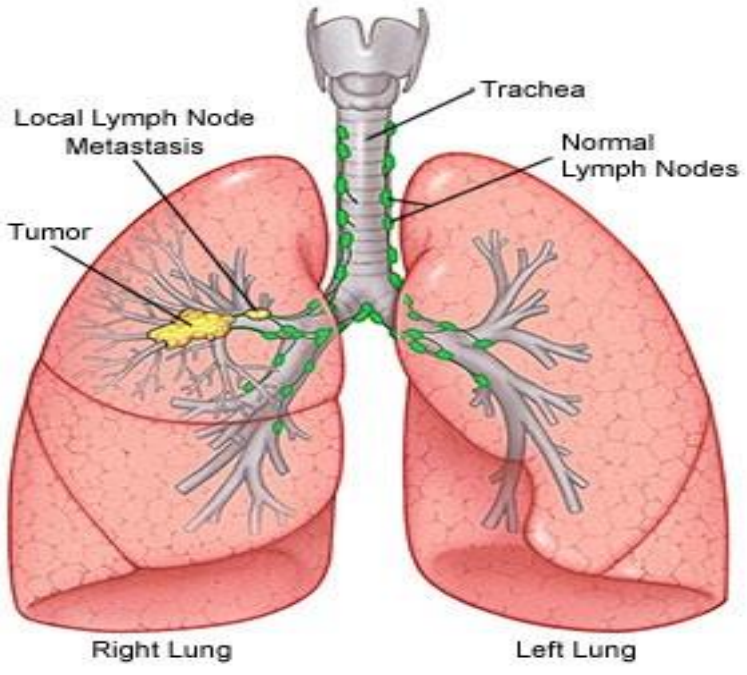

FIGURE 4: Lymph node metastasis and tumors in Lungs
("Lung Cancer Facts".medicine.net)

[2.5] HEAD AND NECK CANCER:

This cancer was named collectively to the cancers that develop in throat, mouth, lips, nose, salivary glands and larynx. It mostly develops in squamous cells (lining of the mucosal, moist surfaces inside one's head or neck). Categorization of this cancer is done on the basis of the area in which they develop [61]. Majorly 5 types of head and neck cancer are there categorized according to the body part it is developed in:

1) Para nasal and Nasal cavity sinus cancer,

2) Hypo pharyngeal or Laryngeal cancer,

3) Salivary gland cancer

4) Oropharyngeal and Oral cancer

5) Nasopharyngeal cancer [62].

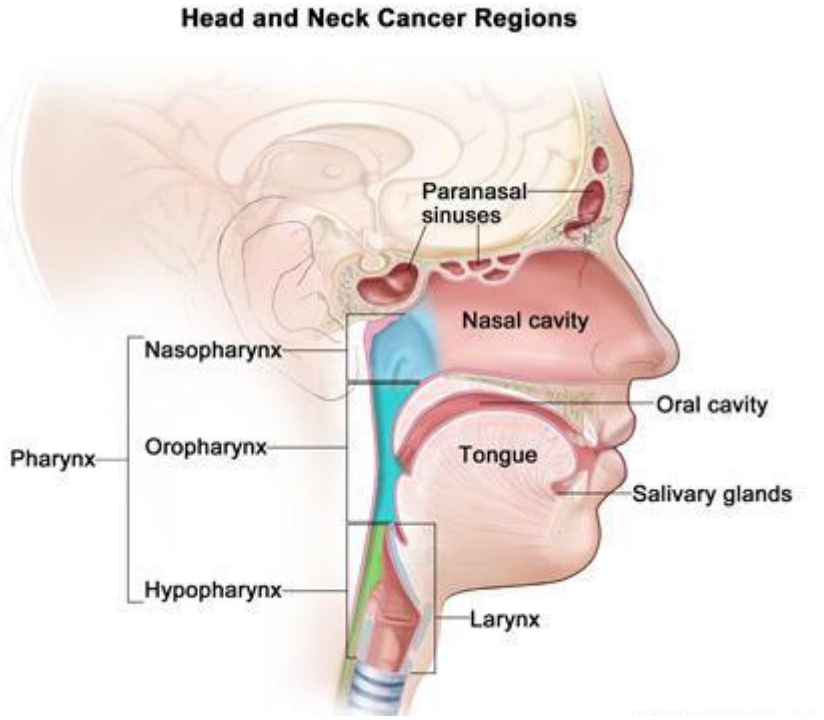

FIGURE 5: Region where Head and Neck Cancer occurs usually ("Head and Neck cancers",NCI. *March29, 2017.*)

(1) PARA NASAL AND NASAL CAVITY SINUS CANCER: Para nasal means near the nose. This type of cancer develops in the tissues of para nasal sinuses and nasal cavity. Squamous cell carcinoma is the major type of Para nasal and nasal cavity cancer. The risk of Para nasal sinus and nasal cavity can increase by being exposed to certain chemicals or dust [64]

(2) LARYNGEAL CANCER (or Hypo-pharyngeal cancer): Laryngeal cancer or Hypo-pharyngeal cancer is an infrequent cancer in which the cancerous cells tend to grow in the voice box: larynx. There are 3 parts of larynx:

- Supra-glottis: it is the tissue present above the glottis,
- Glottis: it is the middle part containing vocal cords,
- Sub-glottis: it is the tissue present below the glottis connecting trachea that transports air to the lungs.

Laryngeal cancer can develop in any part of larynx from Supra-glottis, Glottis, Sub-glottis, but it usually develops in the Glottis. Smoking tobacco and alcohol drinking are the major risk factors of Laryngeal cancer [63].

(3) SALIVARY GLAND CANCER: Salivary gland cancers are uncommon pathologic agents that are formed from major salivary gland tissues and minor salivary gland tissues that is located throughout the HNC region [67].

(4) OROPHARYNGEAL AND ORAL CANCER: Oral cancer develops in the oral cavity (mouth), it comprises of gums, teeth, cheeks, lining of lips, or on lips, or some part of tongue, below tongue, bony roof of mouth. Oropharyngeal cancer is generated in other throat parts that is present just at the back of the mouth, called Oropharynx which starts where the oral cavity ends [66].

(5) NASOPHARYNGEAL CANCER: Nasopharyngeal Cancer is nasopharynx carcinoma (NPC). It starts in the upper part of the throat near the base of skull and behind the nose. There are 3 types of NPC:

a)Non-keratinizing undifferentiated carcinoma- the most common type of NPC,

b)Non-keratinizing differentiating carcinoma.

c)Keratinizing differentiating carcinoma [65].

Risk factors of Head and Neck cancer: As there have been numerous researches proving that HNC were caused by the combination of various reasons as well as the factors of risk. However, the primary reasons still remain tobacco and alcohol abuse. Excessive usage of the carcinogenic product results in developing malignant or benign type tumors of oropharynx and hypopharynx. Consumption of high quantity of alcohol in a short time is much more dangerous than consuming fewer quantities in a long period of time [68]. Patients that are affected with cancer causing (Human Papilloma virus) with increase in risk of getting

effected from HNC, cancer due HPV develops majorly in oropharynx [72]. Similar kinds of factors which can result in HNC include environmental, genetic, or lifestyle habits [68-70].

Diagnosis of head and neck cancer:

There are a no. of tests that can be done to diagnose Head and neck cancer like:

1. Endoscopy,
2. Biopsy,
3. Panoramic radiograph,
4. X-ray, Barium swallow,
5. Molecular testing of Tumor,
6. Ultrasound,
7. Computed tomography (CT or CAT) scan,
8. MRI (Magnetic resonance imaging),
9. Bone scan,
10. Positron emission tomography (PET) or PET-CT scan [73].

Treatment of Head and Neck Cancer:

Since it's a highly chronic infection which results in death and in case not taken care of soon and efficiently, following most common options of treatment have been reported:

- **Chemotherapy:** It is the utilization of medications to devastate malignant growth cells, by shielding the disease cells from developing, isolating, and making more cells. A chemotherapy routine, or timetable, for the most part comprises of a particular number of cycles given over a set timeframe. A patient may get 1 medication at once or a blend of various medications given simultaneously.

- **Photodynamic Therapy:** PDT is a two-phase treatment that consolidates light vitality with a medication (photosensitizer) intended to demolish destructive and precancerous cells after light enactment.

- **Radiation Therapy:** This treatment utilizes a controlled portion of radiation to murder or harm disease cells. The radiation is focused at the malignant growth, and treatment is painstakingly wanted to do as

meager mischief as conceivable to solid body tissue close to the disease. Radiation treatment r for head and neck malignant growths it is normally given remotely.

•**Surgery:** In some cases, a doctor will remove tumors and cancerous cells. The kind of medical procedure you have relies upon the size and position of the malignant growth, and whether it has spread. The point of medical procedure is to evacuate the malignancy totally. Specialist will likewise do everything conceivable to limit the progressions that medical procedure may cause to your discourse, gulping, breathing, or facial appearance.

•**Targeted Therapy:** Targeted treatment is a treatment that objectives the disease's particular qualities, proteins, or the tissue condition that adds to malignant growth development and endurance. This sort of treatment hinders the development and spread of malignant growth cells while restricting harm to solid cells.

Various studies are underway to find the effective treatment of HNC [74].

Prevention:

Avoidance from the danger of being affected by any type of HNC is the most effective way of avoiding your probabilities to have this carcinoma.

(a) Discontinuing stuff abuse: Tobacco and its by-products are the leading risk factor of HNC, avoiding its usage and spreading awareness about its side effects may be of great help avoiding HNC and fight against this lethal disease.

(b) NO Alcohol- Other chief reason for maximum HNC cases is alcohol. It produces toxicity in the body which leads to development of lethal carcinogens that may develop cancer in larynx or oral cavity. Stopping or even reducing the consumption of alcohol helps in lowering the risks of getting such fatal cancers.

(c) Regular Dental check-ups: To prevent from developing this disease, regular check-ups at dentists can avoid development of such unwanted formation in the oesopharynx region.

(d) Good Oral Hygiene: Taking good care of your teeth and using sterilizing mouth washes is a good, easy and effective way to reduce the risk of developing HNC [75].

[2.6] Single Nucleotide Polymorphism (SNP):

SNP is alteration of a nucleotide at a particular position within the genome which is present in more than 1% population. Such variations take place due to mutation or because of genetic evolutions. With SNPs, hereditarily relations with various maladies were found and even today broad examinations are under advancement for realizing the conceivable transformation changes that is dependable to cause illnesses such as Alzheimer's infection and sickle cell anaemia, and etc.

SNP is the bio-makers which help to define the susceptibility patterns in the genome of population from a particular region of geography, or from some specific ethnicity towards a disease. The research carried out on SNPs could further help to check for treatments possible and a solution for eradication of genetically associated diseases.

In case of cancer, there are many researches which depict some possible mutations related to the susceptibility of the population of getting the disease. Other applications of SNPs related research are the benefits included for newer research fields like pharmacogenetics, biomedical researches and Forensics [76, 77].

From a clinical point of view, SNPs are expected symptomatic and restorative biomarkers in numerous malignant growth types. SNPs are situated in various locales of genes, like, promoters, exons, introns, regulatory regions such as 5′-and 3′ UTRs. Therefore, adjustments in gene expression and their impact on disease depend upon the region where the SNP is present. The promoter region of SNPs influences gene expression by affecting transcription factor binding site, DNA methylation and histone alterations. The exonal SNPs influence malignant growth susceptibility by suppressing gene translation and transcription. SNPs in introns produce splice variations of transcripts and enhance or disturb binding and capacity of long non-coding RNAs (lncRNAs). SNPs in the 5′-UTR affect translation, though SNPs in the 3′-UTR affects microRNA (miRNA) binding. SNPs in areas that are situated a long way from the genes diminish or improve quality of binding of long-range cis-regulatory factors [78].

[2.7] MEVALONATE PATHWAY AND FDFT1

Mevalonate pathway is a major metabolic pathway which synthesises sterol isoprenoids like cholesterol and non-sterol isoprenoids – ubiquinone or and dolichol, and lipids. Mainly this pathway is taken as a hallmark for cholesterol biosynthesis study. However, lot of studies are still going on this for its implication to relate to pathological roles [79].

Mevalonate pathway or the MVA pathway which makes use of Acetyl-CoA for producing steroids and isoprenoids which are in relation with the growth and formation of the tumor along with its further progression. MVA pathways produced some sterols which are important in the terms of progressive cancer. Body genes which that regulate the expression of MVA pathway enzymes are under the control of SREBP (sterol regulatory element bindning protein) transcription factor.

The modification of in oncogenic proteins for malignancy of cells brings about uncontrolled MVA pathway [80].Mevalonate or MVA were synthesized from the 3-hydroxy-3-methylglutaryl (HMGCoA) coenzyme by HMG-CoAR (HMG-CoA reductase) enzymes, which act as a limiting agent in a MVA pathway. Further, the MVA is broken down in Geranayleranyl Pyrophospate (GPP) and Farnesyl Pyrophospate (FPP). The two enzymes have a primary part in protein prenylation process that further tends to impact the functions of a cell like proliferation, growth, or division. Various researches depict that MVA pathways are upregulated in different types of cancer like multiple myeloma, lymphoma, leukaemia, along with prostate, oesophageal, pancreatic, hepatic, and breast cancers. Different causes exist that interrelates such diss-regulation of the pathways which results in tumors leading to progressive cancers like p53 mutation, HMG-CoAR mutation and cleavage-activating protein SCAP (SREBP) in the form of regulators, decreased AMPK activation, PKB/Akt activation, as well as activation of transcription factors like, HIF-1 and SREBP which are few of the factors responsible among many other similar factors. In addition to this many guanosine triphosphate hydrolases like RAS and RHO is helpful in the tumorigenesis processes because of its isoprenylation [81-84].

FDFT1:

Outcomes of the MVA pathway and bio synthesis of the cholesterols could be differentiated by producing 2 by-products that is GPP and FPP. Farnesyl Pyrophosphate with the help of SQS (squalene synthase) enzymes is converted into squalene. The FDFT1 gene encodes for SQS enzymes that are situated on 8th chromosome at 8p23 position. The average size of the product of this gene is near about 47kDA and has a crucial part in MVA pathway as this is a regulatory gene of an enzyme in a pathway. FDFT1 gene is expressed mainly in hypothalamus and liver despite of the normal expression of the entire body. The FDFT1 gene promoter has multiple elements in regulating the sterol and has multiple isoforms with 8 exons among them.

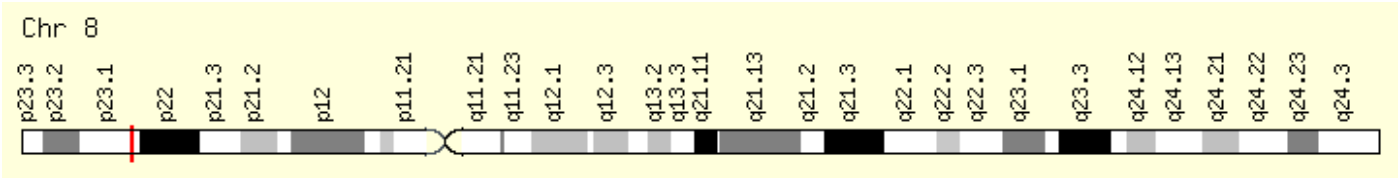

FIGURE 6: Genomic location of FDFT1 gene on Chromosome 8
(Source: GeneCards.org)

FDFT1 rs2645424 has an important role which was also researched on to check the role in other diseases as well like:

- **Chronic Hepatitis C (CHC) -** In this study, rs2645424 was studied by RT-PCR in 478 patients with CHC who finished treatment with peg-IFN-α-2a/ribavirin. All had a pretreatment liver biopsy. It was found out that the minor allele in FDFT1 was related with an advanced edge fibrosis in the non-steatotic yet not in the steatotic subgroup. This may reflect distinctive metabolic pathways in fibrosis movement for steatotic and non-steatotic patients with CHC [85].
- A case-control study was conducted on genome-wide association studies (GWAS) identified variants related to **Nonalcoholic Fatty liver Disease (NAFLD).** In this study, distinction between variants recognized by 7 GWAS recognized variants including FDFT1 rs2645424 was done to check whether it was associated with NAFLD in children of chinese population and it was found out that FDFT1 rs2645424 was not associated with the NAFLD in this population [86]
- Santoro et al performed a study on 229 obese children and adolescents of different ethnic groups (Caucasian, African-americans and Hispanics) and reported that this variant is significantly associated with driving the individual's predisposition towards **hepatic injury** [87].
- In yet another GWAS study performed in 2010, clinical, laboratory, and histologic information from 236 non-Hispanic white ladies with **NAFLD** was examined. 324,623 single nucleotide polymorphisms (SNPs) from the 22 autosomal chromosomes were analyzed. This study reported an association of variant rs2645424 with the score of NAFLD activity [88].

SNP rs2645424 is an intron variant. By mentioning and checking all the above factors of the research, further rs2645424 FDFT1 relationship is been studied with different cancers such as lung cancer, and Head and Neck cancer for the very first time be performing a case-control study on the people of India belonging to Himachal Pradesh.

[2.8] PCR-RFLP:

For performing genotype analysis as well as discovering the FDFT1 gene variant susceptibility in the patients and its relation with people with common cancer, PCR-RFLP could be applied. PCR is polymerase chain reaction technique which is used to amplify the desired region of DNA. The method used for finding out the distinctiveness and differences in a given sequence of DNA is Restriction Fragment Length Polymorphism (RFLP). Such patterns of differentiation were used for finding the differences among different organisms and such patterns visible were also named as, VNTRs (Variable Number of Tandem Repeats). It can be used for differentiating among the intraspecies and interspecies of the organisms. Alec Jeffreys, an English Scientist on 1984 came up with RFLP in his study in hereditary analysis. Enzymes like Restriction endonucleases which cuts the DNA on particular locations like the restricted locations. As the variations in genetics are different in different species or organisms, hence the length of fragmented DNA would accordingly differ. Hence, in this technique, First of all the region containing the variant is amplified using specific set of primers. After the amplification of the region of gene containing the variant, restriction digestion reaction using specific restriction endonuclease enzyme is performed to check the presence or absence of the selected variant is done. The results are finally viewed by using agarose gel electrophoresis.

[3] MATERIALS AND METHODS:

Population Study: The research that was to be carried out here was supposed to be on people belonging to a northern state of India, named Himachal Pradesh. Some cancer samples shall be used, with some control samples and all these samples should match as per the geographical distribution as well as the age in entire Himachal Pradesh State. As for this research the DNA will be isolated and must be carried out with proper consent and certifications from the patients. After this step the blood samples should drawn from the patients and accordingly labelled.

Sampling: Under proper supervision sampling should be carried out and with a proper consent signed by the participating patients. Sterilized needles should be used to draw blood with 5ml blood drawn from every patient which should be stored in vials coated with EDTA and placed in cold storage on lower than -20°C temperature so as to avoid DNA degradation and blood clotting.

Isolation of Genomic DNA: From the blood samples collected the DNA should be isolated with the help of salting method and then were separately stored in individual vials in -20°C temperature.

The given below shows different steps followed in the DNA isolation process by Salting Out Technique.

Step 1: To 300 micro litres of blood sample, 900 micro litres of RBC lysis buffer should be added (3 times of blood sample) and kept on incubation on a rocker at RT for proper lysis of the RBCs.

Step 2: Centrifugation is to be done at 13000 rpm for 1 min, we will obtain a white creamish pellet of WBCs.

Step 3: Discard of the supernatant, the WBC pellet will be thoroughly suspended in300 micro-litres TE buffer at pH 8.0 using vortexing machine. Then 20 micro-litre 10% of SDS solution should be added and incubated at 56 degree Celsius on dry bath.

Step 4: 150 micro-litres of 7.5M ammonium acetate should be mixed vigorously for about 1 minute per sample. Centrifugation of the mixture at 13000 rpm at RT for 15 mins should be done which will separate the proteins as pellet as precipitate.

Step 5: The clear supernatant should be transferred to a frest sterile micro-centrifuge tube. To this chilled absolute ethyl alcohol should be added (2 times the volume of supernatant). And rocked gently for precipitation of genomic DNA.

Step 6: The genomic DNA precipitates should be centrifuged at 13000rpm for 10 min. to pellet at the bottom of tube. The latter should be subsequently washed to 150 micro-litres of 70% ethanol and air dried at RT for about 10-15 minutes.

Step 7: 100 micro-litres of TE buffer pH 7.3 should be used to dissolve the dried DNA pellet by incubating at 65 degree celcius for 10 min. The dissolved DNA should be finally stored at -20 till further use and or for running it on agarose gel with using Ethidium Bromide and 0.8% Agarose**.**

PCR-RFLP: The optimization of annealing temperature and primer concentration for amplification of DNA should be done with the help of gradient PCR. Gradient PCR should be done using six different temperature levels at the optimization time. After the optimization of annealing temperature, the PCR reaction should be carried out after which its genotyping should be carried out. After that, results should be visualized on agarose gel with suitable luminescence dyet like, EtBr. After DNA genotype amplification of the samples are carried out, restriction digestion will be carried out using Pst1 enzyme. The pattern of RFLP will be visualized by agarose gel electrophoresis.

After that, analysis of genotypes will be done to check whether the variant rs2645424 predisposes the studied population towards the chosen cancer type.

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