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A Review on Understanding the Connecting link between Genes and Cancer and the Involvement of Genetics in Cancer Development

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ABSTRACT

Cancer genetics is the scientific discipline that investigates the genes and pathways that drive the development of cancer. Cancer geneticists use several approaches including the analysis of the genomes of cancer patients, and that of their tumors, to identify cancer genes. These studies are performed along with experiments in in vitro and in vivo models to decipher the mechanisms that drive tumorigenesis. Cancer geneticists aim to identify cancer genes, that when mutated, contribute towards cancer development by promoting tumor cell growth and by conferring upon a neoplastic cell the ability to evade the cell cycle and apoptosis checkpoints that might normally control their growth. Cancer geneticists are also interested in the networks and pathways that contribute to tumor development and the way cancer genes work together to market tumor evolution.

***Keywords*-**cancer, cancer genes, tumor cell growth, apoptosis, neoplastic cell, tumor evolution, cancer geneticists.

I. INTRODUCTION

Genes play a twofold role in cancer development for an individual. It not only predisposes individuals to the disease in the metabolic and biological sense, but it also predisposes individuals to certain behaviors that might enhance their risk for cancer by making them susceptible to an unhealthy lifestyle. It is important to disseminate this known information and expand the research and resources that support genetic research in cancer. Awareness of the twofold genetic component in cancer can empower individuals into making healthy lifestyle choices. It is important to utilize this information, allow predisposed individuals to apply extra caution in determining lifestyle habits, and avoiding hazardous environmental elements. Identifying the biased individuals will enable them to take preventive measures like intervening with chemotherapeutics, chemo-preventive agents, nutritional additives, vaccines or even genetic engineering [1]. While the mutagenic processes that result in the evolution of a cancer may generate a signature that can be used to define the repair processes that are operative and the nature of environmental carcinogens to which a person may have been exposed, not all somatically acquired mutations are drivers of tumorigenesis. Driver mutations may be identified either by the frequency at which a gene is mutated in a cancer type or by functional validation using *in vivo* or *in vitro* models, where a gene's ability to induce a cancer cell-like phenotype is assessed [2].

Over the past several decades, a large number of cancer genes have been identified and characterized. This has led to improvements in genetic testing and diagnostics, as well as more accurate prognostic information. Advances in cancer genetics are just beginning to impact cancer therapeutics. The impending complete sequencing of the Human Genome Project, in combination with further advances in techniques such as microarray expression analysis, will dramatically enhance progress within the study of cancer genetics. Sites of chromosome breakage, once identified, will be readily cloned based on the known genes residing at the specific chromosomal positions. Similarly, an enlarging pool of RFLP markers will be facilitating the localization of genes linked to familial cancer syndromes. The recognition of a familial pattern of disease may result in further investigation of potentially affected patients and families. Therefore, the goal will be effective screening and management recommendations. Also, consultation of chromosomal maps to delineate genes closely linked to a particular site may substitute for laborious positional cloning methodology [3,17].

II. HOW DO GENES WORK?

Genes control how our cells work by making proteins. The proteins have specific functions and act as messengers for the cell. Each gene must have the correct instructions for making its protein. This allows the protein to perform the correct function for the cell. All cancers begin when one or more genes in a cell mutate [4]. It creates an abnormal protein or might prevent a protein's formation. An abnormal protein provides different information than a normal protein. This can cause cells to multiply uncontrollably and become malignant. There are 2 basic types of genetic mutations:
Acquired Mutations: They are the most common cause for cancer. They occur from the damage caused to genes

in a particular cell during a person's life. For example, it could be a breast cell or a colon cell, which then goes on to divide many times and form a tumor. Cancer that occurs because of acquired mutations is called sporadic cancer. Acquired mutations are not found in every cell in the body and they are not passed from parent to child. Factors that cause these mutations include:

- Tobacco
- Ultraviolet (UV)radiation
- Viruses
- Age

Germline Mutations: These are less common. A germline mutation occurs in a sperm cell or egg cell. It passes directly from a parent to a child at the time of conception. As the embryo grows into a baby, the mutation from the initial sperm or egg cell is copied into every cell within the body [4]. Since the mutation affects reproductive cells, it can pass from one generation to the other. Cancer caused by germline mutations is called inherited cancer. It accounts for about 5% to 20% of all cancers.

III. MUTATIONS AND TUMORIGENESIS

Mutations happen often and they might be beneficial, harmful, or neutral. This depends upon the location in the gene where the change occurs. Typically, the body corrects most mutations. A single mutation will likely not cause cancer. Usually, cancer occurs from multiple mutations over a lifetime. That is why cancer occurs more often in older people since they have had more opportunities for mutations to build up in their bodies.

Cancer genetics has classically relied on the candidate-gene approach, detecting acquired or inherited changes in specific genetic loci accumulated in a single cell, which then proliferates to produce a tumor composed of its identical clonal progeny. During the early steps of tumor formation, mutations that lead to an intrinsic genetic instability, allow additional deleterious genetic alterations to accumulate. These genetic changes confer selective advantages on tumor cell clones by disrupting control of cell proliferation.

The identification of specific mutations that characterize a tumor cell has proved invaluable for analyzing the neoplastic progression and remission of the disease. The emergence of cancer cells is a by-product of the necessity for continuous cell division and DNA replication to maintain organ functionality throughout the life cycle. The highly heterogeneous nature of tumors, each composed of multiple cell types, lead to the formulation of the "cancer stem cell" hypothesis, which says that only a subpopulation of cancer cells is able to maintain self-renewal, unlimited growth, and capacity for differentiation into other, more specialized cancer cell types [4,5]. Figure 1 shows the detail schematic representation of mutation that leads to tumor formation.

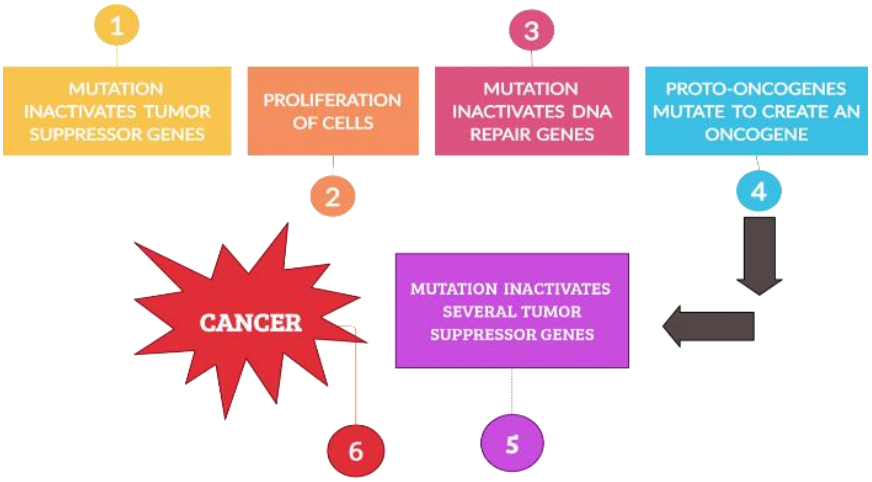

Figure 1: The stepwise processes of Cell Mutation leading to Tumorigenesis.

Cancer stem cells display bona fide stem cell markers, in contrast to other cancer cells present in the tumor, which do not have tumorigenic potential. In fact, fewer than 1 in 10,000 cells present in human acute myeloid leukemia are capable of reinitiating a new tumor when transplanted into animals.

Cancer stem cells have been identified in many solid tumors in the brain, colon, ovaries, prostate and pancreas, suggesting that more effective cancer therapies would target these self-renewing cells, rather than the tumor as a whole. The cancer stem cell concept differs from the original clonal evolution hypothesis, which states that every cell in a tumor mass is capable of self-renewal and differentiation, and suggests that detecting and targeting subtle genetic and epigenetic differences that distinguish cancer stem cells may provide a more effective avenue to intervention in disease progression [5].

IV. TYPES OF GENES LINKED TO CANCER

Many of the genes that contribute to cancer development fall into these broad categories:

Tumor suppressor genes: The mutation of tumor suppressor genes is thought to contribute to tumor growth by inactivating proteins that normally act to limit cell proliferation [8]. These are protective genes and they normally limit the cell growth by:

- Monitoring how quickly cells divide into new cells
- Repairing mismatched DNA
- Controlling when a cell dies

When a tumor suppressor gene mutates, cells grow uncontrollably. And they may eventually form a tumor. Examples of tumor suppressor genes include BRCA1, BRCA2, and p53 or TP53.

Germline mutations in BRCA1 or BRCA2 genes increase a woman's risk of developing hereditary breast or ovarian cancers and a man's risk of developing hereditary prostate or breast cancers. They also increase the risk of pancreatic cancer and melanoma in both men and women. The most commonly mutated gene in people with cancer is p53 or TP53 [4]. Induction of p53 by DNA damage may act to cause cell cycle arrest or cell death by altering the transcription program of damaged cells [8]. More than 50% of cancers involve a missing or damaged p53 gene. Most p53 gene mutations are acquired. Germline p53 mutations are rare, but patients who carry them are at a higher risk of developing many different types of cancer [4,6].

Oncogenes: These are gain-of-function mutations of normal regulatory genes or proto-oncogenes. Originally discovered in retroviruses initiating a variety of animal and avian cancers, oncogenes are believed to be important contributors to human carcinogenesis [9]. These turn a healthy cell into a cancerous cell. Mutations in these genes are not known to be inherited. Together with other oncoproteins or in the absence of tumor suppressor gene products, oncogenes contribute to human cancer formation by supporting accelerated proliferation, de-regulating cell cycle control or blocking apoptosis. Two common oncogenes are:

- HER2, a specialized protein that controls the growth of cancer and its spread. It is found in some cancer cells. For example, breast and ovarian cancer cells.
- The RAS family of genes, which makes proteins involved in cell communication pathways, cell growth, and cell death [4,9].

DNA repair genes: These fix mistakes that are made when DNA is copied. Many of them function as tumor suppressor genes. BRCA1, BRCA2, and p53 are all DNA repair genes. If a person has an error in a DNA repair gene, mistakes remain uncorrected. The mistakes can then become mutations which may eventually lead to cancer, particularly mutations in tumor suppressor genes or oncogenes. Mutations in DNA repair genes may be inherited or acquired. Lynch syndrome is such an example of the inherited kind. BRCA1, BRCA2, and p53 mutations and their associated syndromes are also inherited.

V. THE ROLE OF GENETICS IN CANCER DEVELOPMENT

Several genetic changes distinguish cancerous cells from normal cells, as demonstrated by the large number of chromosomal abnormalities found in an individual cancer cell. However, a limited collection of genetic alterations will confer increased proliferative and survival properties on the cells. Those rare gene defects which result not only in substantial expansion of a clone but also in increased risk of malignant conversion of its progeny, are said to be rate- limiting for cancer development. The low frequency of mutations that can initiate the cancer process in a tissue is a critical bottleneck. However, after successful passage through this bottleneck, the generation of a highly expanded population of precancerous cells is assured, and subsequent somatic mutations in one or more of these precancerous cells are likely. These additional somatic mutations underlie progression to frank malignancy [10].

Presently, the role of genetics in cancer development is still being unearthed. Virtually every cancer occasionally runs in families and, each cancer type is an occasional complication of some hereditary condition, usually a rare one. So, while, most cancers have some genetic determinants, few common cancers can be largely attributed to a single major mutant gene. But for breast, colon, prostate, ovary, and lung cancer, rare mutant genes that enormously increase the risks have been discovered (Fig 2).

Meanwhile, research has already established that genetic predispositions to cancer has increased the risk for developing cancer significantly (in some cases, a mutation on a specific gene can increase breast cancer risk by a startling 80%). Knowledge of genetic predisposition to cancer and corrective lifestyle changes can help an individual avoid the chances of developing the disease, and in some cases avoiding it all together. Cancer cases may fall under one of the three categories: inherited, familial and sporadic. Inherited cases of a dominant type include the occurrence of cancer throughout generations, frequently a result of direct germline mutation, passed successively from parent to offspring. Approximately 4% (1 to 20%, dependent of type) of cancer cases can be characterized as inherited cancers. Larger percentage of cancers are familial and involve mutations on multiple susceptibility genes that increase an individual's risk for cancer. Familial cancers appear to run in the family, yet the frequency of the cancer does not follow the same pattern as those for

inherited cancers [1]. Since multiple genes are involved in familial cancers, an irregular frequency of occurrence takes place. As a result, it is far more difficult to predict the pattern. Usually, families with familial pattern of cancer have higher than normal prevalence, however not in a predictable pattern of incidence. Sporadic cancer cases are those where an individual randomly develops cancer in the absence of any familial pattern.

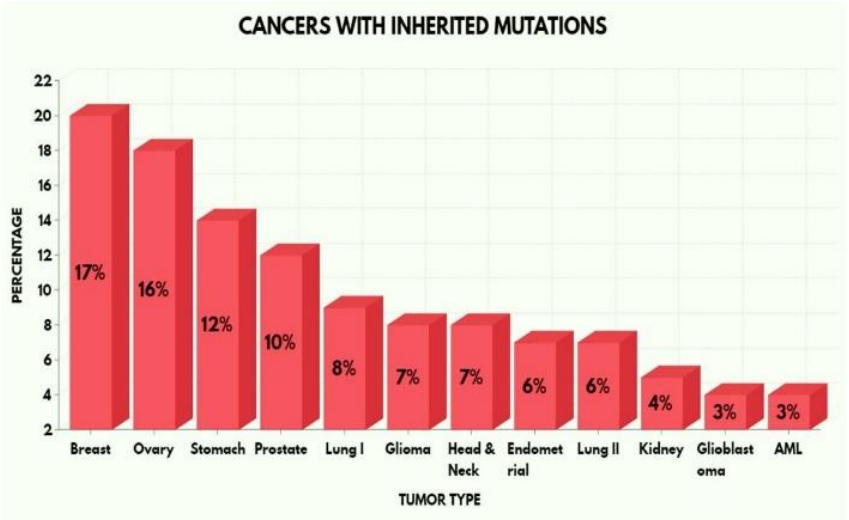

Figure 2: Graph showing the percentages of various inherited cancer mutations

In high income countries, some more commonly factors include habits such as tobacco and alcohol consumption, excessive exposure to sunlight, chemicals and toxins. In low to middle income countries, the culprits of cancer are frequently infectious agents such as viruses, parasites and bacteria, where the available treatment, if any, is inadequate to counter the infection. In many cases, untreated chronic disease can lead to cancer. Genetic predisposition or certain genetic mutations that make an individual susceptible to cancer development, has been known to play a major role in many cancers. For instance, familial retinoblastoma is almost entirely dependent on genetic predisposition and the environment has very little impact on it [7].

VI. CHALLENGES IN UNDERSTANDING CANCER GENETICS

Researchers have learned a lot regarding the working of the cancer genes, but many cancers are not linked with a specific gene. Cancer involves multiple gene mutations. Moreover, some evidence suggests that genes interact with their environment. This further complicates our understanding of the role genes play in the development of cancer. Researchers continue to study how genetic changes affect cancer development. This knowledge has led to enhancements in cancer care, including early detection, risk reduction, the utilization of targeted therapy and survival. Further studying cancer genetics may help doctors find better ways to:

- Predict a person's risk of cancer
- Diagnose cancer
- Treat cancer

Most cancers (90%-95%) are sporadic and occur by chance. It is likely that only 5%-10% of the disease occurs because of an inherited predisposition or gene faults. These inherited gene faults, though comparatively rare, can give rise to a high lifetime risk of developing cancer. In families where there is an inherited predisposition, cancer tends to occur at a younger age. The same type of cancer may affect several family members, there might be unusual cancers or two different cancers may affect one family member. It is further thought that a 10%-20% of breast, colorectal and ovarian cancers may be caused by other inherited "medium risk" gene faults which can also give rise to further significant risks [4,11].

Most people (even people with cancer) do not need this type of genetic testing. It's usually done when family history suggests there's a cancer that might be inherited. Sometimes after a person has been diagnosed with cancer, the doctor will do tests on a sample of cancer cells to look for certain gene changes. These tests can sometimes give information on a person's prognosis and help determine the certain type of treatment that might be useful [12,13].

VII. WHO SHOULD GET TESTED?

The ideal candidate for initial genetic testing will be an individual with an early-onset syndrome cancer who is in the direct line of hereditary descent, and will be the most likely candidate to carry the family's pathogenic mutation. If that mutation can be identified in a likely syndrome carrier, it is then possible for other at-

risk members of the family to have "mutation-specific testing." Although the initial genetic diagnosis is limited by technical considerations, once the index mutation is identified in the proband, confirmatory testing is cheaper and is nearly 100% sensitive and specific when performed by the same reference laboratory. [16,13]

People who essentially need to be tested to prevent, cure or change their lifestyles to stop the spreading of cancer are:

- Several first-degree relatives (mother, father, sisters, brothers, children) with cancer
- Many relatives on one side of the family who have had the same type of cancer
- A cluster of cancers in a family that are known to be linked to a single gene mutation (such as breast, ovarian, and pancreatic cancers in a family).
- A family member with more than 1 type of cancer
- Family members who had cancer at a younger age than normal for that type of cancer
- Close relatives with cancers that are linked to rare hereditary cancer syndromes
- A family member with a rare cancer, such as breast cancer in a male or retinoblastoma
- Ethnicity (for example, Jewish ancestry is linked to ovarian and breast cancers)
- A physical finding that's linked to an inherited cancer (such as having many colon polyps)
- A known genetic mutation in one or more family members who have already had genetic testing

One needs to know the family history and the kinds of tests are available for detection. For some types of cancer, no known mutations have been linked to an increased risk. Other cancer types may have known mutations, but there's no way to test for them yet.

VIII. BENEFITS, RISKS AND LIMITATIONS OF GENETIC TESTING

Genetic testing can help determine if one has certain genetic variations that place him/her at an increased risk of developing cancer. It's often done when one has a family or personal history of certain types of cancer. Cancer genetic screening is extremely important not only for determining cancer susceptibility but also establishing the best treatment option for cancer patients based on their tumor genetic profile. There are several genetic tests used in clinical practice to determine the susceptibility and treatment of common types of cancers affecting the Western populations, including breast and ovarian cancers, CRC, and lung cancer [19]. There are many benefits to genetic testing. For example, a negative test result may offer some peace of mind. Or, a positive result could help that person to start taking steps that can prevent cancer from occurring.

Genetic testing for cancer can have several potential benefits. These can include:

- ***Peace of mind:*** If a certain type of cancer runs in a family, a negative test result can give a person belonging to that family a peace of mind that he/she haven't inherited certain variants.
- ***Preventative actions:*** Learning that one has a variant that increases their cancer risk, can help them to take preventative steps early and look out for potential cancer symptoms, if they develop.
- ***Family testing:*** It is always possible that immediate family members can learn about their cancer risk from a particular person's results. It may also encourage them to get tested [15].

While genetic testing for cancer has several benefits, there are also some risks associated with it as well. The potential risks associated with genetic testing for cancer include:

- ***Psychological impact:*** Receiving a result that's positive or inconclusive, as well as deciding whether to share the result with family members, may lead to high levels of stress or anxiety.
- ***Guilt:*** It is possible that one might feel guilty after receiving a negative result for a variant that's present in other members of his/her family.
- ***Cost:*** Genetic testing can be expensive and may not be covered by some health insurance plans.

Limitations: Genetic testing does have limitations. A positive test result doesn't mean with certainty that one will develop cancer. Meanwhile, a negative test result does not mean that the person can never develop cancer over the course of his/her lifetime [14]. A healthcare professional or a genetic counsellor works with people to help them decide if genetic testing is right for them. If one decides to get tested, the professionals walk him/her through what the results mean as well as guide and discuss steps for further proceedings be it treatment or changes in lifestyle [14,15,18].

IX. PREVENTION

Individuals are often inherently at a higher risk for cancer due to their genetic composition, and this predisposition needs to be taken into account in conjunction with the person's lifestyle habits while evaluating a person's overall risk for cancer [7]. The availability of genetic tests for BRCA gene mutations prompted cancer geneticists to give information about genetic risk and to assess many women with a personal or family history of breast or ovarian cancer to inform them of preventive measures. These consist mainly of breast self-examination, mammography screening, chemoprevention and prophylactic surgery (mastectomy, oophorectomy) [20]. Knowledge of such a predisposition

would allow the individual to make healthier lifestyle choices so as to decrease the existing risk of the disease. For individuals affected by cancer, which is a significant percentage of the population, this information is critical to the prevention and avoidance of cancer.

X. DISCUSSION AND CONCLUSION

The increasing evidence of genetic linkage to cancer onset and development makes it an important part of research and public health which can no longer be overlooked. While all these genetic testing technologies are available, most people do not have access to these resources, especially in low to middle income countries. Governments can strengthen their capacity to provide the adequate basis for genetic services progressively in order to lay a foundation for the increasing role of human genetics in patient care and disease prevention. To assist in this process, the Human Genetics Programme is constructing a Genomic Resource Centre (GRC) to provide tools for health professionals, policy makers, NGOs, and patients. The goal of the GRC is to establish a consensus among the existing technologies that are available, to pull together all resources and networks of information, and to allow everyone to have access to this database. Hence, even while low to middle income countries may not have the resources to conduct extensive research on their own, the information is still available and accessible to them.

By coupling awareness of genetic predispositions with choices of a healthy lifestyle, individuals will have much more authority over their health. To accomplish this, public health must deviate from the current one-track approach that solely analyses environmental factors and take on a new strategy that cooperates genetics with environment. The aim is to significantly reduce the number of cancer cases. Concurrently, more resources need to be devoted to research in pharmacogenetics and gene therapy, where existing data shows that within these two fields, there is a promising future for the treatment of cancer.

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