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REVIEW ARTICLE


# Oral Cancer-related Inherited Cancer Syndromes: A Comprehensive Review

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## ABSTRACT

Oral squamous cell carcinoma is the most common malignancy of the oral cavity, which is usually preceded by a myriad of oral potentially malignant disorders (OPMDs). In the classification of OPMDs, inherited cancer syndromes (ICSs) were proposed as one of the categories. Inherited cancer syndromes are genetic disorders in which inherited genetic mutation in one or more genes predispose the affected individuals to the development of cancer and may also cause its early onset. Many of these syndromes are caused by mutations in tumor suppressor genes, oncogenes, and genes involved in angiogenesis. General dental practitioners frequently come across OPMDs in their day-to-day practice. It becomes of paramount importance to have knowledge about these rare but prognostically important OPMDs. With this view in mind, in this article, efforts have been made to comprehensively discuss about various ICSs that have higher potential of transformation into oral cancer. The ICSs discussed in this article are xeroderma pigmentosum (XP), ataxia telangiectasia (AT), Bloom syndrome (BS), Fanconi's anemia (FA), and Li–Fraumeni syndrome (LFS), with special emphasis on signs, symptoms, and genetic considerations.

**Keywords:** Ataxia telangiectasia, Bloom syndrome, Fanconi's anemia, Inherited cancer syndromes, Li–Fraumeni syndrome, Xeroderma pigmentosum.

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## INTRODUCTION

With millions of new cases being reported every day, cancer seems to be tightening its grip on to the lives of the people from all over the world. The incidence of this fatal disease is expected to rise fivefold in the near future. The majority of cancers found today are caused by environmental factors, the percentage of which accounts for 90 to 95. These generally include the chemical and physical carcinogens, such as tobacco, diet, microorganisms, radiations and hormonal-related factors. Inherited mutated genes carrying the defect cause the remaining 5% of the cancer cases, and such disorders are called inherited cancer syndromes (ICSs).[1]

Inherited cancer syndromes carrying inherited genetic mutations in one or more genes predispose the affected individuals to the development of cancers and may also cause the early onset of these cancers. Inherited cancer syndromes often show not only a high lifetime risk of developing cancer, but also the development of multiple independent primary tumors.[2] Many of these syndromes are caused by mutations in tumor suppressor genes, oncogenes, and genes involved in the production of blood vessels (angiogenesis).[3]

Cancer inheritance can be explained by the Knudson's two-hit hypothesis, which states that the first hit of the gene is the inherited mutation, while the second hit occurs later in life.[4-6] The onset of many of the cases starts with occurrence of potentially malignant disorders. "Oral potentially malignant disorders (OPMDs)" are referred to as all the clinical presentations that carry the risk of cancer including the syndromes associated with a greater than normal risk of malignant transformation. This article

attempts to review all the ICSs that are classified by Sarode et al[7-11] under group III of inherited disorders that do not necessarily alter the clinical appearance of local tissue but are associated with a greater than normal risk of potentially malignant disorders or malignant transformation. All these syndromes included either carry some risk and/or predispose the individual to cancer development.

General dental practitioners frequently come across OPMDs in their day-to-day practice. It becomes necessary to have knowledge about these rare but prognostically important OPMDs. Thus, in this article, we have made efforts to comprehensively discuss various ICSs that can show transformation into oral squamous cell carcinoma. The ICSs discussed in this article are ataxia telangiectasia (AT), Bloom syndrome (BS), Fanconi's anemia (FA), Li–Fraumeni syndrome (LFS), and xeroderma pigmentosum (XP), with special emphasis on signs, symptoms, and their genetic considerations.

## Ataxia Telangiectasia

Ataxia telangiectasia (Louis-Bar syndrome) is a neurodegenerative disease characterized by poor coordination and telangiectasia.[12,13] It is caused by a defect in the ataxia telangiectasia mutated (ATM) gene.[14-16] The signs and symptoms are usually noted first in the early childhood when the child just begins to walk. Although they begin walking at a regular age, they usually wobble while walking or standing still.[17,18] As the age advances, certain anonymous disabilities can be detected, which include oculomotor apraxia, auditory problems, distorted speech, swallowing problems, pneumonia, upper respiratory tract infections, sinusitis, and bronchitis.

### *Clinical Manifestations*

Ataxia telangiectasia is an autosomal recessive disorder that can be characterized by progressive cerebellar ataxia with degeneration of purkinje cells, hypersensitivity of fibroblasts and lymphocytes to ionizing radiations, a 61-fold and 184-fold increased cancer incidence in white and black patients respectively, nonrandom chromosomal rearrangements in lymphocytes, thymic hypoplasia with cellular and humoral (immunoglobulin (Ig)A and IgG2) immunodeficiencies, elevated serum levels of alfafetoprotein, premature ageing, and endocrine disorders, such as insulin-resistant diabetes mellitus.[19]

Ataxia is evident at an early age, but gradually worsens as the age advances. Telangiectasia appears over the sclera of the eyes, giving them a specific bloodshot appearance[16] and the body parts exposed to the sun are also affected.[20] Detrimental involuntary movements also occur. At the age of 15, most of the neurologic problems stop progressing. Dysphagia and drooling is particularly observed in young children with dysarthria and vitiligo[20] along with low levels of certain Igs and low T-lymphocyte count.[21]

An increased incidence of cancer, primarily lymphomas, and leukemias is generally observed.[22] A recent study revealed a twofold increased risk of breast carcinoma in women with a single mutated copy of the ATM gene.[23,24] The use of radiation therapy and chemotherapy drugs as a mode of treatment proves to be extremely fatal and toxic for people suffering from this disorder as these have a mechanism of action that works in a manner similar to radiomimetic drugs.

### *Genetic Considerations*

Ataxia telangiectasia is caused by a defect in the ATM gene located on chromosome 11q22-23.[25] The ATM gene manages the cellular response to various stressful conditions, which also includes the double-strand breaks in deoxyribonucleic acid (DNA). The protein which is normally synthesized by this gene plays certain vital roles, which include to recognize a break in the sequence of DNA's nucleoproteins, to fix the break by the recruitment of proteins, and to stop the cell from synthesizing newer DNA molecules until the damage is repaired. Based on this peculiar feature, AT is also known as a genome instability syndrome and a DNA repair disorder.[26]

The disease is genetically heterogeneous, with four complementation groups that have been suspected to represent different genes. Ataxia telangiectasia mutated, which has a transcript of 12 kilobases, was found to be mutated in AT patients from all complementation groups, indicating that it is probably the sole gene responsible for this disorder. The discovery of ATM should enhance understanding of AT and related syndromes and may allow the identification of AT heterozygotes, who are at an increased risk of cancer.

## Bloom Syndrome

Bloom syndrome, which is also known by the name of Bloom–Torre–Machacek syndrome, after the scientists who discovered it, is an autosomal recessive disorder. The diagnostic features of this disorder include short stature, genomic instability, and an early predisposition to the development of cancer.[25-30] The syndrome was for the first time discovered by Bloom.[31] Its incidence is more in the people of European Jewish background.[32]

### *Clinical Manifestations*

The hallmark features of the disease include short stature and a rash. The rash appears on the face that develops early in childhood. An exposure to the sun is necessary for the development of the rash. The rash is erythematous

scaly and has an infiltration of cellular components. It may appear anywhere on the area of the face, including the cheeks, lips, and the surface of nose. Other skin features include patches of skin that are lighter or darker than the surrounding areas. The pigmentation involves certain distinct spots known as the cafe-au-lait spots. Telangiectasia is also observed on the skin and eyes.[32] Also observed are certain facial features, such as a long and a narrow face, prominent outgrown nose and ears, a high-pitched voice, and micrognathism. Since the individual also has moderate immune deficiency, deficiency in certain classes of Ig, pneumonia, and other infections and inflammations are quite a common finding.

People with BS also have an increased risk of cancer. Since an overlap in the functions of the mutated proteins is well marked in FA and BS, common features are observed among these related disorders. Leukemias, lymphomas, carcinomas, synchronous and metachronous cancers have an early onset in the lives of these affected individuals. The development of the cancer can occur at any age; than one type of cancer is also seen. A recent survey conducted proved that the individuals suffering from this disorder have a shortened life expectancy, approximately being 27 years old.[33]

Also, people with BS are usually small in both height and weight from birth, and rarely exceed 5 feet of height in adulthood. Bloom syndrome affects the fertility of the affected individuals.

### *Genetic Considerations*

Mutations in the BLM gene cause BS.[34] The BLM gene provides necessary instructions to produce a protein from RecQ helicases. Helicases play an important role in replicating the DNA, preparing the cell for cell division, and repairing the damaged DNA. The BLM protein helps to prevent excess sister chromatid exchanges and maintains the stability of the DNA during the copying process.

The mutations in the BLM gene result in the absence of functional BLM protein. Hence, the frequency of sister chromatid exchange is about 10 times higher than average. Also, chromosome breakage occurs more frequently in affected individuals. All of these changes are associated with gaps and breaks in the genetic material that impair normal cell activities. Without the BLM protein, the cell is unable to repair DNA damage caused by ultraviolet light, which results in increased sun sensitivity. Genetic changes that allow cells to divide in an uncontrolled way lead to the cancers that occur in people with BS.[35] The US Food and Drug Administration has authorized marketing of a direct to consumer genetic test. The test is designed to identify healthy individuals who carry a gene that could cause BS in their offspring.[36]

## Fanconi's Anemia

Fanconi's anemia, an infrequent genetic disorder, occurs as an outcome of a defect in the group of proteins, which play a major role in the repair of the damage caused to the DNA. It was first discovered by the Swiss pediatrician Guido Fanconi, hence the name Fanconi's anemia. According to a recent survey conducted, about 60% of the patients have developmental disabilities and congenital defects, which include short stature and endocrine problems, abnormalities of the kidneys and ears, while as high as 75% of patients have severe abnormalities of the arms, eyes, head, and also of the skin.[36-40] This genetic disorder has an occurrence rate of 1 in 160,000 individuals worldwide, with a common finding among the people of Ashkenazi Jewish descent, the Roma population of Spain, and black South Africans.[38]

### *Clinical Manifestations*

Fanconi's anemia has a drastic effect on many parts of the body. During childhood, short stature and skin pigmentation, which include characteristic café-au-lait spots, are a common finding. The other complications include bone marrow failure, physical abnormalities, organ defects, as well as an increased risk of certain cancers.[41]

In most of the cases reported so far, the patients with this disorder have a bone marrow failure,[42] wherein the bone marrow fails to produce new cellular entities to meet the demands of the body. Thus, common complications include various anemias, most common being the aplastic anemia. Also, well-marked neutropenia and thrombocytopenia are a common finding. The decreased levels of red blood cells fail to carry enough oxygen, so, fatigue and tiredness are well observed. The chances of development of myelodysplastic syndrome are quite high.[39]

Around 50% patients develop certain physical abnormalities, which include hypopigmentation, malformed thumbs, forearms and kidneys, skeletal problems and other defects of the urinary tract, gastrointestinal abnormalities, and heart defects. People with this condition may have abnormal genitalia and certain malformations of the reproductive system. Additional signs and symptoms can include abnormalities of the central nervous system, hydrocephalus, and microcephaly. Also, an increased risk of developing acute myeloid leukemia and tumors of the head, neck, and face region is quite ubiquitous.[43]

The unique sensitivity of FA cells to the clastogenic effect of DNA cross-linking agents, such as diepoxybutane can be used to facilitate the diagnosis. Also, therapy includes the administration of androgens and the

hemotopoietic growth factors, which have a success rate of about 75% in the patients. A more reliable and successful cure includes hematopoietic stem cell transplantation.[44]

### Genetic Considerations

Fanconi's anemia is an autosomal recessive chromosomal breakage disorder in which five complementation groups (FA-A through FA-E) have so far been distinguished. Complementation groups in FA are likely to represent distinct disease genes, two of which (FAC and FAA) have been cloned. There are three new groups identified, FA-F, FA-G, and FA-H, providing evidence for a minimum of eight distinct FA genes.[45]

## Li–Fraumeni Syndrome

Li–Fraumeni syndrome named after Li and Fraumeni,[46] is better known as the sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome. The disease was recognized and described after the analysis of medical records and death certificates of 648 children suffering from rhabdomyosarcoma.[47] It is well characterized as an infrequent and an autosomal dominant disorder. Multiple metachronous primary neoplasms are also observed in several family members. Li and Fraumeni suggested that the occurrence of diverse neoplasms in these families might represent a counterpart of the tendency for a single individual to develop multiple primary tumors and that these families represented a previously undescribed familial cancer syndrome, with transmission suggestive of an autosomal dominant gene.

### Clinical Manifestations

Li–Fraumeni syndrome is characterized by diverse amounts of cancers, early onset of cancer, and the development of multiple cancers throughout the life of the individual. It can be described as a cancer predisposition syndrome that is generally associated with the development of the tumors, including soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumors, adrenocortical carcinoma, and leukemias.[48] Certain age-specific cancer risks have also been calculated. This syndrome till date has been reported in more than 400 LFS families. According to a research conducted, the risk of developing any invasive cancer is 50% by the age of 30, while it rises up to 90% by the age of 70. The early onset of breast cancer is a familiar finding, followed by soft and hard tissue sarcomas and glioblastomas. The females affected by this disorder have 100% risk of developing breast cancer, while the affected males account for a 75% risk.[49] The mean age of 60 accounts for the development of breast cancer in females. Certain other tumors, such as melanoma, Wilm's tumors, gonadal germ cell, choroid plexus, colorectal, and prostate cancers, are found to be associated with this disorder as well. The diversity of neoplasms observed suggests pathogenesis, which differs from hereditary cancers occurring in single organs or tissues.

Li–Fraumeni syndrome can be diagnosed by meeting the established clinical criteria in patients with a germline pathogenic variant in TP53 regardless of family cancer history. As high as 70% of the individuals diagnosed clinically have an identifiable germline pathogenic variant in TP53, the only gene so far identified in which mutation is definitively associated with LFS.

Li–Fraumeni syndrome can be diagnosed once the three criteria are met: The patient diagnosed with a sarcoma at an age below 45 years, a first-degree relative is diagnosed with any cancer at an age below 45 years, and another first-degree or a second-degree relative has been diagnosed with any cancer at an age below 45 years or with a sarcoma at any age and also includes the Birch criteria and Eels criteria.[50,51]

Certain management options are recommended for malignancies in patients with LFS. In breast cancer cases, mastectomy is recommended than lumpectomy to reduce the risk of development of a second primary breast tumor. An increased risk for radiation-induced second primary tumors should be kept in mind while treating these patients.

### Genetic Considerations

Li–Fraumeni syndrome is an autosomal dominant disease in which an inherited abnormal copy of the TP53 gene is seen.[52] The second allele of TP53 is either somatically mutated or deleted, leaving cells with no functional gene product. The mutations can be *de novo* or acquired from one of the parent's germ cells. The gene TP53 is located on chromosome 17p13.1, although mutations at two other locations (one at 1q23 and the CHEK2 locus at 22q12.1) have been postulated. In the absence of the normal activated p53 protein, cells containing damaged DNA can survive and proliferate, leading to malignancy.[53]

## Xeroderma Pigmentosum

Xeroderma pigmentosum was first described by Moriz Kaposi and Ferdinand Hebra in 1870. Xeroderma pigmentosum is an autosomal recessive genetic disorder of DNA repair in which the ability to repair damage caused by ultraviolet light, is deficient.[53] Individuals with this disorder have an increased risk of developing skin cancer, and about 50% of children with XP develop it by the age of 10 years. Most patients with XP develop multiple skin cancers occurring on the face, lips, eyes, eyelids, scalp, and on the tip of the tongue. Studies

suggest that people with XP may also have an increased risk of other cancers.[54]

### Clinical Manifestations

The disorder mostly affects the eyes and areas of skin which are exposed to the sun. The signs of XP, usually, appear in infancy or early childhood. Many affected children develop a severe sunburn after spending just a few minutes in the sun.[53] The sunburn causes redness and blistering that can last for weeks. By the age of 2 years, almost all affected children develop freckling of the skin of face, arms, and the lips. The skin is dry and scaly with irregular dark spots on it.

The eyes of people with XP are painfully sensitive to ultraviolet rays from the sun.[50] If the eyes are not protected from the sun, they may become bloodshot and irritated, and the cornea becomes cloudy. The eyelashes may fall out, and the eyelids become thin and turn inward or outward. Xeroderma pigmentosum is also associated with noncancerous growth on the eye. About 30% of individuals with XP develop progressive neurological abnormalities, which include hearing loss, poor coordination, difficulty in walking, movement problems, loss of intellectual function, difficulty in swallowing and talking, and seizures.

An important part of the treatment involves avoiding exposure to sunlight. Therapies include whole-body cryotherapy and ice pack therapy. Fluorouracil or 5-FU is used in the treatment of cancer.[54]

### Genetic Considerations

There are seven complementation groups plus one variant form XP-V. Xeroderma pigmentosum variant (XP-V) cells carry out normal nucleotide excision repair processes which are defective in XP, while the replication of ultraviolet-damaged DNA is affected in XP-V.[55]

Many of the genes affected in XP play a role in nucleotide excision repair.[56-58] The proteins produced from these genes play a variety of roles in this process. This leads to failure in recognizing and unwinding DNA damage, in excising and replacing the abnormal DNA sections. Mutations in POLH gene cause XP-V. Accumulation of damaged DNA is the major feature of XP, which can cause neurological problems. Damage to the DNA of neural cells can also occur, but factors responsible for it are still unknown.

## CONCLUSION

Inherited cancer syndromes are routinely diagnosed on clinical picture and laboratory findings, which are used to locate individuals at high risk and to educate them about their susceptibility to a variety of cancers. Counseling sessions are mandatory, which leads to positivity in the life of the individual with ICSs. The most important aspect of the treatment is to take care of the malignancy associated with the syndromes. For this purpose, the common diagnostic tests performed include the biopsy of the tumor, blood tests that recognize the specific tumor markers, bone marrow biopsy, chest X-rays, complete blood count, computerized tomography scans, magnetic resonance imaging scans, liver function tests, etc. The treatment varies based on the type of the cancer and the stage in which it is present. If the surgery fails to remove all the tumors, the rightful choice of the treatment may include radiations, chemotherapy, or both. Certain tumors require a combination of surgery, radiations, and chemotherapy.

Although no permanent cure has been found till date, advancement of the technology has led to a wide center of active research by experts. The rate of mortality is high but nevertheless, advances have been made to increase the life span of individuals with cancer-inherited syndromes.

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