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Oral Manifestations of Genodermatoses

Richa Wadhawan[1], Yehoshuva Reddy [1], Padma Rajan[2], Anubhav Jain [3], Arjun Deo Singh [3]

[1]Department of Oral Medicine, Diagnosis & Radiology, Institute of Dental Education & Advance Studies, Gwalior, and Madhya Pradesh, India.
[2]Department of Periodontics, Institute of Dental Education & Advance Studies, Gwalior, and Madhya Pradesh, India.
[3]Interns, Institute of Dental Education & Advance Studies, Gwalior, and Madhya Pradesh, India.

Corresponding Author: - Richa Wadhawan

Abstract: Genodermatoses consign to an inherited skin disorder associated with structure andfunction. Several genodermatoses present with multisystem involvement lead to increased morbidityand mortality. Many of these disorders are rare and also have oral manifestations, called oralgenodermatoses. This article provides a focused review of molecular basis of importantgenodermatoses that affects the oral cavity and also has prominent associated dermatologic features.In several conditions discussed here, the oral findings are distinct and may provide the first clue of anunderlying genetic diagnosis. Many of these disorders are rare. However, the recognition of their skinfindings is important not only for the initiation of appropriate dermatologic therapy, but also for thedetection of other associated abnormalities in these frequently multisystem disorders, includingmalignancy.

Key words: Mucocutaneous lesions, Multisystem disorders, Gene mutations, Oral manifestations, Skin manifestations

Introduction:

Genodermatoses refers to a group of inherited monogenic disorders with skin manifestations. Many of these disorders are rare and also have oral manifestations called oral genodermatoses. During the past decade an unprecedented explosion in molecular biology and genetic research has helped to refine understanding of the pathogenesis of many human diseases [1]. In the post genomic era, unravelling of the genes that are responsible for genetic disorders of epidermal appendages has given new insights into the complex molecular pathways which regulate their development and biological function. Cancer associated genodermatoses like basal cell nevus syndrome, Muir Torre syndrome; Cowden syndrome, Carney complex and Birt Hogg-Dubé syndrome are a group of autosomal-dominant genetic disorders. These have unique cutaneous findings that are reliable marker for the risk of developing internal malignancies [2]. This article provides a focused review of genetic basis of important genodermatoses that affect the oral cavity and also have prominent associated dermatologic feature. In genodermatoses the oral findings are distinct and may provide the first clue of an underlying genetic diagnosis. In these genetic disorders, family members may also be at risk. Molecular genetic testing, when available as an aid for diagnosis and genetic counselling of the patient and their families, is also included in discussion. Hundreds of known genetic disorders affect the mouth and oral mucous membranes. Proposed classification of oral genodermatoses [3].

1. Genodermatoses affecting teeth and dentition

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• Ichthyosis

• Sjogren-Larrson syndrome

• Incontinentia pigmenti

• Ehlers Danlos syndrome

• Focal dermal hypoplasia syndrome

• Gardner syndrome

• Ectodermal dysplasia

• Hyperimmunoglobulin E syndrome (Job syndrome)

2. Genodermatoses affecting periodontium and gingiva

•Ichthyosis

• Sjogren-Larrson syndrome

• Papillon Lefevre syndrome

• Tuberous sclerosis

• Chediak-Higashi syndrome

• Ehlers Danlos syndrome

• Focal dermal hypoplasia syndrome

3. Genodermatoses affecting oral mucosa

• Darier's disease

• Neurofibromatosis type 1 and 2

• Chediak-Higashi syndrome

• Ehlers Danlos syndrome

• Lipid proteinosis

• Focal dermal hypoplasia syndrome

• Multiple hamartoma syndrome (Cowden syndrome)

• Pachonychia congenita

• Epidermolysis bullosa

• Multiple endocrine neoplasia syndrome

• White sponge nevus

4. Genodermatoses affecting jaw bones and facies

• Mccune-Albright syndrome

• Ehlers Danlos syndrome

• Marfan syndrome

• Focal dermal hypoplasia syndrome

• Gardner syndrome

• Basal cell nevus syndrome

• Orofacial digital syndrome type I

5. Genodermatoses causing pigmentation of oral mucosa

• Carney complex

• Neurofibromatosis type 1 and 2

• Mccune-Albright syndrome

• Lipid proteinosis

• Pseudoxanthoma elasticum

• Peutz-Jeghers syndrome

• Congenital erythropoetic porphyria

• Hypomelanosis of ito

• Sturge-Weber syndrome

• Hereditary hemorrhagic telengiectasia

Histocompatibility antigens and disease association: - Human leukocyte antigens (HLA) - are glycoproteins on the cell surface of most nucleated human cells. These differ in subtle ways from person to person and uniquely fingerprint each person's cells. The importance of HLA system has been highlighted by the need to match donors and recipients in the transplantation of human tissues. The HLA region is located on the short arm of chromosome 6, referred to as the major histocompatibility complex (MHC), a person inherits HLA as a set, one set (haplotype) from each parent. There are at least 4 or 5 genetic loci that produce HLA, termed A, B, C, D and DR, and their gene products are called HLA-A, HLA-B,HLA-C,HLA-D, and HLA-DR . The association of an HLA with a given disease means that there is a higher incidence of that antigen in a group of patients with that disease than in a group of people without that disease [4].

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The ways in which the presence of a particular HLA might be involved in the pathogenesis

of a disease are :-

1. Molecular mimicry – i.e. an infective agent may have a similar configuration to HLA, so the agent is then not attacked by the body's defense system.

2. Receptor effects – many chemicals, including drugs and toxins bind to the cell surface before they are taken into the cytoplasm, since HLAs are presented on the cell surface, could modify the binding of these potentially toxic substances.

3. Genetic linkage – the HLA may be close to another gene on the same chromosome that produces a disease, either directly (e.g. due to an enzyme deficiency), or indirectly due to an effect on the immune response , leading to autoimmunity , or abnormally decreased leading to infection . The association between an HLA and a particular disease is rarely absolute. Some skin diseases known to be associated with particular HLA , e.g. dermatitis herpetiformis with B8, Dw3,DRw3, pemphigus with DRw4 , Reiter's disease with B27 , Behcet's disease with B5 , psoriasis with B13,B17,B37,Cw6,Dw7, psoriatic arthropathy (central-B27 , and peripheral Bw38) .

Chromosomal disorders: - Genetic counselling- is advice to parents for an accurate diagnosis and a detailed family history to reduce the risk of chromosomal disorders, by termination of pregnancy, a risk greater than 10% is high, whether a risk of less than 5% is considered low [5].

Dystrophic Epidermolysis Bullosa is a group of phenotypically diverse genodermatoses, widespread blistering, resulting in the development of bullae or vesicles in mucosa or skin in response to minor trauma. It is a chronic mechanobullous disease characterised by auto antibodies against Type VII collagen. The onset of the disease usually is at birth. It is characterized by flat, pink bullae of ankles, knees, hands, elbows and feet in decreasing order of frequency followed by scarring & milia formation. These changes are usually evident before one year of age in about 20% of patients and improvement is seen to occur with age. It is an acquired disease or inherited as either autosomal-dominant or recessive with an incidence of 1/50 000. Specific defect in the attachment mechanisms of the epithelial cells.

Molecular genetics: Most cases of dystrophic epidermolysis bullosa are associated with involvement of anchoring filaments and anchoring fibrils which form an interconnecting network extending from basal keratinocytes across the dermal-epidermal basement membrane to the underlying dermis. Mutations of the gene coding for type VII collagen (COL7A1) of anchoring fibrils have been identified. Dystrophic specific mutations in the genes encoding keratin 5 and keratin-14 have been identified as being responsible for most of the simplex types. Mutations in the genetic codes for laminin-5, type XVII collagen and alpha-6 bete-4 integrin have been documented for the junctional types. Dystrophic types appear to be caused by mutations in the genes responsible for type VII collagen production.

Clinical features The initial lesions are vesicles or bullae. The bullae rupture, resulting in erosions or ulcerations that ultimately heal with scarring. Appendages such as finger nails may be lost.

Histopathology - The simplex form shows intraepithelial clefting by light microscopy. Juntional and dystrophic forms show subepithelial clefting. Electron microscopic examination, which is still considered the diagnostic “gold standard.” Clefting at the level of the lamina lucida of the basement membrane in the junctional forms. Below the lamina densa of the basement membrane in the dystrophic forms. [6]

Oral manifestations: Teeth are not affected but 20% of patients manifest oral bullae and milia.

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These milia are epidermoid cyst developing in areas of previous bulla formation. Oral manifestations are typically mild, with some gingival erythema and tenderness [7].

Peutz-Jegher's Syndrome (PJS) It is an autosomal dominant inherited condition characterized by gastrointestinal hamartomatous polyps and tan to dark brown or blue maculae on skin and oral mucosa. Polyps may cause intussusceptions as an important clinical finding. A study by Boardman et al., reported that patients with Peutz-Jegher's Syndrome have 9.9 times increased risk for intestinal cancer compared to general population. Thus, screening for intestinal cancer comprises an important part of management for these patients [8].

Oral manifestations: The brown pigmented macules are present at birth or usually noted at early childhood. Pigmented lesions are seen on skin around the lips and the vermilion zone of the lips is a very common feature. Intra orally, the lesions are usually brown pigmented, painless patches on the buccal mucosa, tongue or labial mucosa. Microscopically, these lesions show mild acanthosis with elongation of rete pegs, and increased number of melanocytes and the adjacent keratinocytes filled with melanosomes [9].

Molecular genetics: The gene associated with Peutz-Jegher's Syndrome is LKB1/STK11 (serine/threonine-protein kinase 11, which is also known as LKB1) at the tumour suppressor gene located on chromosome 19p13 [10]. People with PJS have a 50% chance of passing on the mutation to each of their children [10].Usually; this mutated gene is acquired from one of their parents. Blood testing is available commercially that can detect the mutated STK 11 gene causing Peutz-Jegher's Syndrome [10].

Neurofibromatosis (NF) is a neurocutaneous disorder inherited as autosomal dominant trait. It is classified into two distinct types, neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2). NF1, also known as von Recklinghausen disease, is characterised by the presence of multiple café-au-lait spots. It is defined as oval shaped light brown patches greater than 0.5 cm in diameter, multiple cutaneous neurofibromas, axillary or inguinal freckling, Lisch nodules, optic glioma, a distinctive osseous lesion, such as sphenoid dysphasia, or thinning of the long bone cortex with or without pseudoarthrosis. NF1 affects 1 in 3500 people worldwide. NF2, also known as bilateral acoustic neurofibromatosis, characterized by bilateral vestibular schwannomas involving the superior vestibular branch of the eighth cranial nerve and lesions on the brain and spinal cord. NF2 are relatively infrequent. Tumours of the auditory nerves that lead to hearing loss, is usually the first symptom of the disease [11].

Oral manifestations: Oral involvement is seen in 4-7% cases of NF. Oral soft tissue neurofibromas are discrete with overlying normal mucosa having varying colour ranging from normal mucosal colour to red or sometimes yellow. They are located in the soft tissues such as the cheek, palate, tongue, floor of the mouth and lips. The tongue being the most commonly affected site.

Superficial neurofibromas of tongue gives fissured appearance, whereas the deep seated tumors give an appearance of macroglossia. Tumours also occur on the gingival and buccal mucous membrane and ones that occur within the periodontal membrane lead to the migration of teeth. Neurofibromas have also been noted within the jaw and appear as radiolucent areas on radiographic examination [12].

Molecular genetics: Neurofibromatosis type 1 is a genetic condition caused by mutation on chromosome 17q11.2. The gene products being neurofibromin 1 which activate ras-GTPase activating enzyme (GAP) expressed in cells and is involved in cellular signal transduction. Neurofibromatosis type 2 is caused due to mutation on chromosome 22q12.2, the gene

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product is Neurofibromin 2 also called merlin, a cytoskeletal protein [20]. Both NF-1 and NF-2 are autosomal dominant genetic disorders, meaning only one copy of the mutated or deleted gene is required to affect the individual. A child of a parent with NF-1 or NF-2 and an unaffected parent will have a 50%-100% chance of inheriting the disorder, depending on whether the affected parent is heterozygous (Aa) or homozygous (AA) for the trait ("A" depicts the affected dominant allele, while "a" depicts the recessive allele [13].

MEN's Syndrome (MEN IIB) syndromes are group rare autosomal dominant genetic disorders associated with neoplasm and malignancy of endocrine gland. Two main types of MEN have been identified. MEN- I is characterized by the combination of tumors of the pituitary glands, islets of pancreas and hyperparathyroidism. MEN-II is characterized by the combination of multiple pheochromocytomas and medullary thyroid carcinomas. MEN -II is sub divided into two phenotypes IIA and IIB. MEN-IIB is distinguished from other MEN syndromes because of its association with physical characteristics other than the endocrine findings.

The physical characteristics include thickened corneal nerves visible by slit lamp examination, a 'wide-eyed' facies, Marfanoid body habitus with joint laxity and mucosal neuromas. It is also known as Mucosal Neuroma Syndrome or Wagen-Mann Froboese Syndrome [14].

Oral manifestations: The oral sub mucosal neurofibromas produce characteristic diffuse or nodular swellings in the oral cavity. This feature is pathognomonic of this entity and because of this, the entity is so known as "multiple mucosal neuroma syndrome''. This oral manifestation is often the first clue to the syndrome at early age. Mucosal neuromas may be found on the dorsal surface of tongue, palate, buccal mucosa and pharynx. The tongue neurofibromas appear crenated or notched. Pedunculate symmetric nodules on the buccal mucosa behind each lip commissure have been described as pebbly or blubbery. The palate may be high and arched. All of the findings in MEN IIB are generally thought of as asymptomatic and benign [15].

Molecular genetics: All three phenotypes of MEN are associated with oncogenic point mutations of RET proto-oncogene on chromosome locus 10q11.2. This gene encodes a receptor-type tyrosine kinase. Multiple endocrine neoplasia IIB is inherited as autosomal-dominant manner. Its ligand, the glial cell line derived neurotropic factor (GDNF) forms a signalling complex with the alpha type of the GDNF receptor. DNA testing for RET mutation should be performed soon after birth in all children at risk. Paternal inheritance is noted in half of affected individuals with MEN IIB which are de novo or new mutations Cowden's Syndrome (Multiple Hamartoma Syndrome) [16].

Cowden syndrome a rare genodermatosis also called "Cowden's disease" and "Multiple Hamartoma Syndrome". It is an autosomal dominant inherited disorder characterized by multiple tumor-like growths called hamartomas arising from all germ layers and an increased risk of cancer of breast, thyroid, endometrium, and renal system. The hamartomas are characterised by mucocutaneous flat topped papules involving the oral, nasal, intestinal mucosa. Patients with Cowden's syndrome have an increased risk of developing several types of cancer, including cancers of the breast, thyroid and uterus. Palmoplantar keratosis, vitiligo, neuromas, xanthomas and café au lait spots are additional skin findings reported infrequently association with Cowden's disease.

Oral manifestations: Oral findings are present in 80% of patients and may serve as an important clinical marker in early diagnosis. Oral hamartomas occur mainly on gingiva, buccal and palatal mucosa. The oropharynx, larynx and nasal mucosa may also be involved. The typical appearance of multiple, coalescent, flat topped

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mucosal papules have been described as cobblestone-like and are seen in 40% of patients [17].

Molecular genetics: Mutations in the PTEN gene is the cause for Cowden syndrome. Autosomal dominant inherited mutations in the PTEN gene with chromosomal locus at 10q23.3 have been found in about 80% of patients. PTEN is a tumour suppressor gene, which helps to control the growth and division of cells is mutated leading to the formation of tumors [18].

Basal cell nevus syndrome (Nevoid basal cell carcinoma syndrome/Gorlin syndrome)

It is a rare heritable neurocutaneous disorder passed down through families in autosomal dominant fashion. The syndrome characterized by disorders of skin, ocular, bones, nervous system, genitourinary and cardiovascular systems. The condition causes an unusual skeletal abnormalities and a higher risk of skin cancers. The hall mark of Gorlin syndrome is development of multiple Basal Cell Carcinomas (BCCs) of skin at or around puberty. Other important features include jaw cysts, nervous system condition followed by calcification of falx cerebri and lead to: blindness, deafness, mental retardation and seizures. Various developmental skeletal abnormalities such as bifid rib, scoliosis, kyphosis are seen. Other types of tumors can also occur in Gorlin syndrome, such as medulloblastoma and benign ovarian fibroma tumors.

Oral manifestations: Multiple jaw cysts, odontogenic keratocyst and osseous anomalies like cleft palate are main oral manifestations. Cleft palate and jaw cysts can lead to abnormal tooth development or jaw fractures [19].

Molecular genetics: The gene linked to the syndrome is PTCH1gene localized to 9q22.3. The gene is passed down through families as an autosomal dominant. If the PTCH1 pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at risk is possible. New basal cell skin cancers can be prevented by avoiding the sun and using sunscreen creams. Patients with this condition are very sensitive to ionizing radiation such as X-rays so should be avoided [20].

Gardener's syndrome (familial colorectal polyposis) is a rare autosomal dominant genetic disease characterized by intestinal polyposis, sebaceous cysts and multiple jaw osteomas. It is associated with other skin cysts like epidermoid and desmoid cysts, eye abnormality like congenital hypertrophy of the retinal pigmented epithelium and malignancies like papillary thyroid carcinomas, and adenocarcinomas and also dental abnormalities [21].

Oral manifestations: The enostosis means the bone islands represents a focus of mature compact bone are frequently seen radiographically in the alveolar portions of the jaws seen without evidence of bone expansion. They are completely asymptomatic. Multiple supernumerary and unerupted teeth occur in the incisor, cuspid and bicuspid regions, while the molar areas are rarely affected. Supernumerary teeth are usually peg shaped or otherwise misshapen. Odontomas are the compound type and occur in the same distribution as the supernumerary teeth. Osteomas, which cause a focal expansion of the surface of the jaw bone, can be felt through the skin or oral mucosa and may be large enough to be clinically visible [22].

Molecular genetics: Gardner syndrome is now known to be related to X gene i.e., mutation of APC gene located in chromosome 5q21 (band q21 on chromosome 5) and is transmitted as autosomal dominat trait [23].

Dyskeratosis congenita is inherited as an X-linked recessive trait. It has striking male predilection. Autosomal dominant and autosomal recessive forms are less common. Mutations in the DKC1 gene. The mutated gene appears to disrupt

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the normal maintenance of telomerase. This results in the disease wherein the major protein affected is dyskerin. The X-linked form of this disease may result in specific issues related to dysfunctional rRNA. It can be characterized by classic triad of dystrophy of the nails, lacy reticular cutaneous pigmentation and oral leukoplakia. The patients have high tendency for malignancies and progressive bone marrow failure. The malignancies mainly include the squamous cell carcinomas of head and neck (mainly arising from pre-existing leukoplakia) and in anogenital area.

Other malignancies reported include Hodgkin lymphoma, adenocarcinoma of the gastrointestinal tract, and bronchial and laryngeal carcinoma. Malignancy tends to develop in the third decade of life. Other clinical features include bone marrow failure leading to thrombocytopenia, anaemia, pulmonary complications, ophthalmic abnormalities like continuous lacrimation due to atresia of the lacrimal ducts, testicular atrophy in the male carriers. The patients carrying the more serious forms of the disease often have significantly shortened lifespan [24].

Oral manifestations: Mucosal leukoplakias are seen in approximately 80% of patients can be seen in any mucosa but most frequently seen in oral mucosa. Leukoplakias typically involve the lingual mucosa, buccal mucosa, palate with common site being tongue. The leukoplakia may become verrucous, and ulceration may occur. Patients also may have an increased prevalence and severity of periodontal disease, increased dental caries, thin enamel and hypodontia. Intraorally, the tongue and buccal mucosa develop bullae; these are followed by erosions and eventually leukoplakic lesions. The leukoplakic lesions are considered to be premalignant. Thrombocytopenia is usually the first hematologic problem that develops followed by anemia. Ultimately aplastic anemia develops. Hyperorthokeratosis with epithelial atrophy. As the lesions progress, epithelial dysplasia develops until frank squamous cell carcinoma evolves [25].

Ehlers-Danlos Syndrome (Cutis hyperelastica) is a group of inherited disorders of connective tissue which supports the skin, bone, blood vessels and many other organs of the body. It is caused by a defect in the synthesis of collagen (Type I or III). There are 10 recognized types of Ehlers-Danlos syndromes and depending on the individual mutation; the severity of the syndrome can vary from mild to life threatening.

A group of inherited connective tissue disorders. Problems are usually attributed to the production of abnormal collagen, the protein that is the main structural component of the connective tissue. The production of collagen necessitates many bio-chemical steps that are controlled by several genes. Potential exists for anyone of these genes to mutate producing selective defects in collagen synthesis. There is no cure for the condition and treatment is mainly supportive, including close monitoring of the digestive, excretory and particularly the cardiovascular systems.

It typically affects the joints, skin, and blood vessels. The clinical signs and symptoms are mainly due to faulty or reduced amounts of collagen. The major signs and symptoms include: loose, hyper mobility of joints that are prone to sprains, dislocation, sub luxation and hyperextension [26]. Early onset of osteoarthritis, easy bruising, dysautonomia typically accompanied by valvular heart disease. Flat feet, vulnerability to chest and sinus infections, The vascular type of Ehlers-Danlos syndrome is also associated with fragile blood vessels, includes tearing of the intestine, bleeding and rupture of the uterus during pregnancy. Velvety-smooth skin which may be stretchy, abnormal wound healing and easy scar formation, low muscle tone and muscle weakness, myalgia and arthralgia. The clinical manifestations of EDS in the orofacial region consist of extra-oral and intra-oral manifestations. Extra-oral manifestations consist

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of slender and asymmetric face, retrognathia, scars on the chin and forehead, repeated dislocations of TMJ. The area around the eye includes hypertelorism, epicanthus, strabismus, narrow nasal bridge, shaggy hair, and sagging of the skin. Oral manifestations comprise high arched palate, crowding of teeth, highly fragile mucosa, which is easily ruptured when dental instruments touch them and sutures do not remain in place, usually bruising is evident on the oral mucosa [27].

Molecular genetics: At least 50% of individuals with classic EDS have an identifiable mutation in COL5A1 or COL5A2. Other less common mutations include COL1A1, COL1A2, COL3A1 and TNXB, Enzymes: ADAMTS2, PLOD1. A diagnosis can be made by clinical observation. Both molecular genetics study like DNA analysis and biochemical studies provide accurate tool for diagnosis and therefore the diagnosis. If the disease is running in the family, prenatal diagnosis using a DNA information technique known as a linkage study is possible [28].

Xeroderma pigmentosum (XP) serves as the prototype heritable disease with increased sensitivity to cellular injury. It is a rare, genetically heterogeneous, autosomal recessive disorder characterized by photosensitivity, cutaneous pigmentary changes, premature skin ageing, and the development of various cutaneous and internal malignancies at an early age. Inherited as an autosomal recessive trait. Caused by one of the several defects in the excision repair and/or post replication repair mechanism of DNA. Inability of the epithelial cells to repair ultraviolet (UV) light-induced damage. Markedly increased tendency to sunburn. Atrophy, freckled pigmentation and patchy depigmentation soon follow. In early childhood, actinic keratoses begin developing. These lesions quickly progress to squamous cell carcinoma. The basic defect underlying the clinical manifestations is a nucleotide excision repair (NER) defect leading to a defective repair of DNA damaged by ultra violet (UV) radiation. It is categorized in at least eight complementation groups according to the capacity of the body to repair DNA. These groups (i.e. genetic subtypes) are labelled A through G, plus the XP variant: XPV Groups A, C, D, and variant make up to 90% of XP cases. Group A, for example, has the lowest level of DNA repair and the most neurological manifestations. Frequency of XP has been reported from a low of 1:250,000 in the United States to a high of 1:400,000 in Japan. It is more common in children of consanguineous parents. In 1870, Moritz Kaposi first used the term “xeroderma” to characterize the dry, dyspigmented skin that is the first permanent cutaneous change observed in patients with this disease. It was first described in 1874 by Hebra and Kaposi. 12 years later Kaposi added “pigmentosum”.

The first XP case with neurological signs was described by Dr. Albert Neisser and in 1932, DeSanctis and Cacchione helped coin the term “DeSanctis-Cacchione syndrome” to apply to cases of XP with severe neurological deficiency. UV radiation-exposure to UV light induces DNA lesions. The majority of DNA damage is caused by UVB light, which leads to the most common forms of DNA damage, cyclobutane pyrimidine dimers (CPDs) and 6-pyrimidine-4-pyrimidone photoproducts. Recently, UVA light-induced DNA damage has also been linked to identical mutations. Individuals with XP are unable to remove these lesions, and studies have strongly correlated these errors with early onset of tumorigenesis. It is noteworthy that subjects with XP have a 10 to 20-fold increase in various internal neoplasms that have no UV aetiology compared to the general population, suggesting that the repair of endogenous oxidative DNA damage may also be dysregulated in some subjects with XP. Normally, DNA repair is achieved through nucleotide excision repair (NER) or post replication repair (PRR) [29].Leukoplakia, erythroplakia and squamous cell carcinoma (SCC) of the tip of the tongue,

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actinic cheilitis and SCC of the lips are associated with XP. The precancerous and cancerous lesions of the tip of the tongue, sites seldom affected in the normal population group, are presumed to be induced by UV radiation. This is not a convincing explanation but it is the only one offered. In the general population, SCC most frequently affects the poster lateral and ventral surfaces of the tongue and floor of the mouth of elderly users of tobacco and alcohol, and runs an aggressive course. By contrast XP associated SCC affects the tip of the tongue of persons younger than 20 years of age and runs a slowly progressive course. Chronic desquamative gingivitis was first described by Tomes and Tomes in 1894. However, it was not until the 1930s that Prinz and Merrit first proposed the term of chronic diffuse desquamative gingivitis and first attempted to define the disease process. Chronic soreness is common and can be worse with the intake of spicy foods. The clinical appearance is of gingival erythema and loss of stippling, extending apically from the gingival margins to the alveolar mucosa. The desquamation may vary from mild, almost insignificant small patches to widespread erythema with a glazed appearance. It is now recognized to be mainly a manifestation of a number of disorders ranging from vesiculobullous diseases to adverse reactions to a variety of chemical or allergens. There is no cure for XP. The DNA damage is cumulative and irreversible. Persons with XP must avoid exposure to any sources of UV light including sunlight, fluorescent, halogen and mercury-vapour lights, and must wear protective clothing and UV-absorbing eye glasses, and must use high protection factor sunscreens. Regarding medical care, oral retinoids have been shown to decrease the incidence of skin cancer in patients with XP. Chemical therapy with 5-fluorouracil may be useful for actinic keratoses. A new approach to photo protection is to repair DNA damage after UV exposure. This can be accomplished by delivery of a DNA repair enzyme into the skin by means of specially engineered liposomes. Surgical care includes complete excision of the malignancies associated with XP. Regular surveillance for and treatment of all neoplasms is very important. Regular visits to the dermatologist might be necessary for the purposes of patient education as well as early detection and treatment of any malignancy. Ophthalmologic and neurologic consultations are recommended for XP. It must be remembered that persons with XP who are properly protected from sun-light may suffer consequential vitamin D deficiency, and they should routinely take vitamin D supplements [30].

Tuberous sclerosis complex (TSC): It is an autosomal dominant neurocutaneous syndrome, which may involve multiple organ systems and shows highly variable clinical manifestations. It is also known as Epiloia & Bovrne ville's disease. It represents a genetic disorder of hamartoma formation in many organs, particularly the skin, brain, eye, kidney and the heart. The characteristic skin lesions are angiofibromas, shagreen patch, periangual fibromas and ash-leaf white macules, classically, although not invariably seen in association with epilepsy and mental retardation. The term complex emphasizes the multisystem involvement. It is one of the more common single gene disorders, inherited as autosomal dominant gene on chromosome No.9C, 50% are TSC1 on chromosome 9q34 and 50% are TSC2 link to 16p13 chromosome. Approximately 60-70% of cases are thought to be the result of new mutation. It is classically characterized by mental retardation, seizure disorders and angiofibromas of the skin. Inherited as an autosomal dominant trait. Sporadic and new mutation is also there. These mutations involve either one of two recently described genes [31]. Tuberous sclerosis complex (TSC)-1 (found on chromosome 9) more commonly, TSC-2 (found on chromosome 16).Clinical features facial angiofibromas, ungual or periungual fibromas, hypomelanotic macules (three or more), shagreen patch, CNS hamartomas, cardiac rhabdomyoma, renal

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angiomyolipoma, multiple retinal nodular hamartomas, minor features - multiple renal cysts, hamartomatous rectal polyps.

Oral Manifestations: Fibromatous tumours are occasionally present on the gum, palate and rarely on the tongue, larynx and pharynx. Small pits commonly occur in the tooth in adult patients. Oral manifestations also include enamel hypoplasia and gingival hyperplasia. Awareness of the different oral manifestations of tuberous sclerosis is important to ensure appropriate diagnosis and treatment. Histopathology - Enlarged gingiva shows nonspecific fibrous hyperplasia. Radiolucent jaw lesions consist of dense fibrous connective tissue that resembles desmoplastic fibroma [32].

Gardner's syndrome: - It comprises multiple epidermoid cysts, fibrous tissue tumours, osteomas and polyposis of colon, it is inherited as autosomal dominant gene of variable expressivity, its gene is located on chromosome5q.

Oral Manifestations: Osteomas occur mainly in the maxilla, mandible and sphenoid bone, other bones of skull, and less frequently long bones, usually small and multiple, present in some 50% of cases [33].

Ectodermal Dysplasia is a disorder characterized by partial or complete absence of sweat glands, hypotrichosis and hypodontia inherited as an x-linked recessive gene on chromosome Xq12-q13.Prevalence 1/100000 births, 90% of cases are males, the complete syndrome does not occur in females, but females are a carriers and may show dental defects, sparse hair, reduced sweating and dermatoglyphic abnormalities. Hypohidrotic ectodermal dysplasia X-linked - mapped in the proximal area of the long arm of band Xq-12-q13.1 Decreased expression of the epidermal growth factor receptor. Gene ED1 is responsible. Autosomal recessive - phenotypically indistinguishable from the X-linked form. Gene is located at dl (downless) locus. Hidrotic ectodermal dysplasia GJB6 is the causative gene. This encodes for connexin 30. Located at pericentromeric region of chromosome 13q. For patients with cleft lip/palate-mutation PVRL 1, encoding a cell to cell adhesion molecule/herpes virus receptor. Reduction in number of, sweat gland, hair follicle, and sebaceous gland. Salivary glands may show ectasia of ducts and inflammatory changes [34].

Clinical features: The essential features of the syndrome are absent or reduced sweating, hypotrichosis and total or partial anodontia. In complete forms, the appearance of the patient is distinctive, with prominent frontal ridges and chin, saddle nose, sunken cheeks, thick everted lips, large ears and sparse hair, atrophic rhinitis, persistent foul smelling nasal discharge and crust formation, chronic respiratory infection and hearing problems. Aplasia or hypoplasia of the breast.

Oral Manifestations: The temporary and permanent teeth may be entirely absent, or there may be a few teeth present, the incisors and /or canines are characteristically conical and pointed, jaws are normal, gums may be atrophic, mouth may be dry from hypoplasia of salivary glands and the lacrimal glands may also be deficient [35].

Darier's disease is a genodermatosis of autosomal dominant inheritance causing abnormalities of keratinization. Also known as keratosis follicularis. The gene mutation associated with Darier's is the ATP2A2 gene encoding SERCA-2, a calcium ATPase pump of the endoplasmic reticulum; the resulting disruption in calcium homeostasis in keratinocytes results in poor cell-cell adhesion with subsequent dyskeratosis affecting skin, nails and mucous membranes. The hallmark skin lesion is a hyperkeratotic papule. The diagnosis of Darier's disease is thus dependent on clinical features, family history and a characteristic histopathology. Individuals affected by Darier's disease typically develop manifestations of the disease in the first

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or second decade of life, not at birth. The classic eruption consists of hyperkeratotic, verrucous papules, classically in a seborrheic distribution: scalp, forehead, central face including the nasolabial folds, retroauricular neck, upper trunk, groin and intergluteal cleft. Involvement of intertriginous sites can result in vegetative plaques. Other clinical variants include a cornifying variant, characterized by hypertrophic, vegetative lesions, primarily on the lower extremities, and localized forms in dermatomal, blaschkoid, or linear distribution, suggestive of somatic mosaicism. Some patients may have both variants simultaneously. The classic nail findings include V-shaped nicking, red and white streaking, or longitudinal ridging [36].

Oral lesions, present in 13-50% of patients, include white umbilicated papules found on the palate, gingiva and buccal mucosa, sometimes coalescing into plaques with characteristic cobblestoned pattern. The skin lesions of Darier's are exacerbated by seasonal variation, especially by heat, humidity, UVB light; additional triggers include mechanical trauma, systemic lithium medication, and other chemical exposures. Super infection by staphylococcal or streptococcal bacteria, or by herpes virus, can result in widespread flaring of the disease.

Because the underlying genetic defect cannot yet be corrected, therapeutic strategies attempt to minimize the clinical consequences of abnormal keratinisation and to treat the complications that result from the inherited defect. Systemic and topical retinoids are the mainstay. Because of seasonal exacerbations and partial remissions, therapy should be adjusted accordingly, and vigilant monitoring for super infection with culture-directed antibiotic treatment as needed is critical. Because cutaneous squamous cell carcinoma is a rare complication of Darier's disease, ongoing monitoring for malignancy is also required [37].

Warty dyskeratoma Histopathologically identical to Darier's disease. Hence, the lesion has been termed isolated Darier's disease. Cause is unknown. Appears as a solitary, asymptomatic, umbilicated papule on the skin. Intraoral lesion also develops in patients older than age 40. The intraoral warty dyskeratoma appears as a pink or white, umbilicated papule located on the keratinized mucosa, especially the hard palate, and the alveolar ridge. Dyskeratosis and a supra basilar cleft. Formation of corps ronds and grains is not a prominent feature [38].

Pachyonychia congenita Inherited as an autosomal dominant trait. Specific mutations in the keratin 16 gene-Jadassohn–Lewandowsky type. Mutations of the keratin 17 gene are associated with the Jackso–Lawler form. The oral lesions are seen in the Jadassohn–Lawandowsky form. Whitish plaques on the mucosa of the cheeks & tongue. Marked hyperparakeratosis and acanthosis with perinuclear clearing of the epithelial cells. The free margins of the nails are lifted up because of an accumulation of keratinaceous material in the nail beds. Marked hyperkeratosis of the palmar and plantar surfaces, producing thick, callous like lesions. The rest of the skin shows punctate papules, representing an abnormal accumulation of keratin in the hair follicles. Formation of painful blisters on the soles of the feet after a few minutes of walking during warm weather. Marked hyperparakeratosis and acanthosis with perinuclear clearing of the epithelial cells [39].

Incontinentia pigmenti (**IP**) is a developmental defect involving many structures of ectodermal and mesodermal origin. Inherited as an X-linked dominant trait. Single unpaired gene on the X-chromosome being lethal for most males. Carney (1976), analyzing cases described in the world literature, found the disorder to be present in all races with a 37:1 female-to-male ratio. Inheritance may be dominant with lethality in males, but this has been disputed [40]. Onset of IP skin lesions

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usually occurs at or shortly after birth and is manifested in a series of stages -- first, vesicubullous or erythematous; second, hypertrophic or verrucous; and third, pigmented. Most children with IP have other abnormalities including partial alopecia of the scalp, nail dystrophies, and dental anomalies. Central nervous system abnormalities mental retardation, seizure disorders, motor difficulties, strabismus, cataracts, retinal vascular abnormalities, optic nerve atrophy.

Affected patients show chromosomal instability. Primarily affecting the skin, eyes and central nervous system (CNS), as well as oral structures. Begin in the first few weeks of infancy vesicular stage - vesiculobullous lesions appear on the skin of the trunk and limbs. Spontaneous resolution occurs within 4 months. Verrucous stage - verrucous cutaneous plaques develop, affecting the limbs. These clear by 6 months of age. Hyper pigmentation stage - macular, brown skin lesions appear, characterized by a strange swirling pattern. Atrophy and depigmentation of the skin ultimately occur.

Oral manifestations include oligodontia delayed eruption, hypoplasia of the teeth. The teeth are small and cone-shaped; both the primary and permanent dentitions are affected.

Histopathology: Vesicular stage - intraepithelial clefts filled with eosinophils are observed. Verrucous stage - hyperkeratosis, acanthosis, and papillomatosis are noted. Hyperpigmentation stage - shows numerous melanin-containing macrophages in the subepithelial connective tissue [41].

Conclusion With increasing knowledge of the identities and functions of the genes involved in these inherited skin conditions, many of these disorders are being reclassified, as has occurred recently for epidermolysis bullosa (EB) and the ectodermal dysplasias. Molecular-based diagnostic criteria should help streamline the archaic and sometimes confusing classification systems currently in use. Knowledge of the precise molecular defect(s) underlying hereditary skin diseases will be a necessary step in the development and application of "personalized medicine" approaches to treatment, so that strategies targeting specific genes, pathways, or even mutant alleles may be possible in the near future.

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