Review Article

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# Oral Manifestations and Molecular Basis of Oral Genodermatoses: A Review

Dentistry Section

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## ABSTRACT

Genodermatoses refers to group of inherited monogenic disorders with skin manifestations. Many of these disorders are rare and also have oral manifestations, called oral genodermatoses. This article provides a focused review of molecular basis of important genodermatoses that affects the oral cavity and also have prominent associated dermatologic features. In several conditions discussed here, the oral findings are distinct and may provide the first clue of an underlying genetic diagnosis. The article also emphasises on the prenatal diagnosis, genetic counselling and the treatment oral genodermatoses.

**Keywords:** Dermatologic, Features, Genetic counselling, Inherited disorder, Prenatal diagnosis

## 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 [1].

During the past decade we have witnessed an unprecedented explosion in molecular biology and genetic research that has helped to refine our understanding of the pathogenesis of many human diseases [1]. In the postgenomic 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 discussed here, 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 [3]. 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. Main genodermatoses discussed here with their oral manifestations are:

- Dystrophic Epidermolysis Bullosa.
- Peutz-Jegher's Syndrome.
- Neurofibromatosis.
- MEN Syndrome.
- Cowden Syndrome.
- Gardner's Syndrome.
- Basal Cell Nevus Syndrome.
- Dyskeratosis Congenita.
- Ehlers-Danlos Syndrome.
- Marfan's Syndrome.
- Haemorrhagic Telangiectasia.

### Dystrophic Epidermolysis Bullosa

Dystrophic epidermolysis bullosa is group of heritable genetic diseases characterized by widespread blistering, scarring & milia formation caused by defects of anchoring fibrils [4]. The onset of the disease usually is at birth. Dystrophic epidermolysis bullosa is characterized by flat, pink bullae of ankles, knees hands, elbows and feet in decreasing order of frequency followed by scarring & milia formation [Table/Fig-1] [5]. These changes are usually evident before one year of age in about 20% of patients and improvement is seen to occur with age.

**Oral manifestations:** Teeth are not affected but 20% of patients manifest oral bullae [5,6] and milia [7]. These milia are epidermoid cyst developing in areas of previous bulla formation.

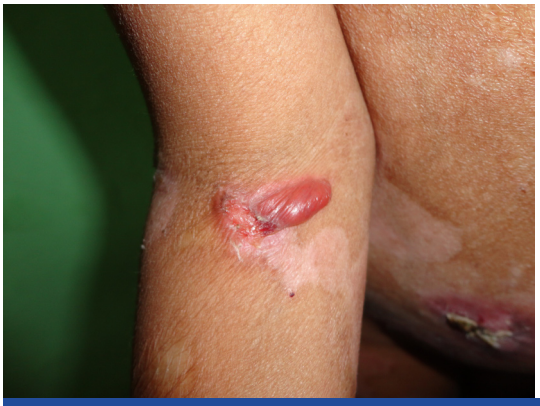
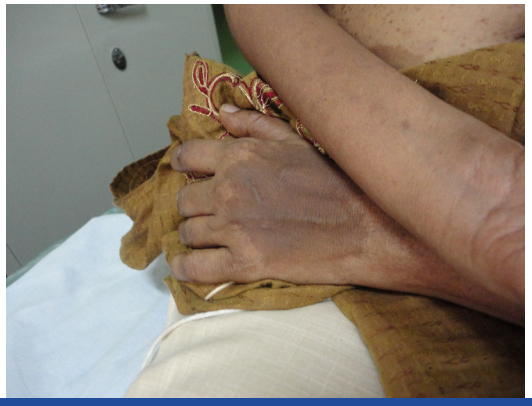
**Molecular genetics:** Most cases of dystrophic epidermolysis bullosa are associated with involvement of anchoring filaments and anchoring fibrils which form an interconnecting network extending from basal keratinocytes across the dermal-epidermal basement membrane to the underlying dermis [4]. Mutations of the gene coding for type VII collagen (COL7A1) of anchoring fibrils has been identified [4].

### Peutz-Jegher's Syndrome

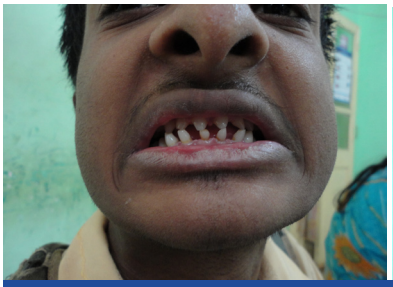
Peutz-Jegher's Syndrome (PJS) is a autosomal dominant inherited condition characterized by gastrointestinal hamartomatous polyps and tan to dark brown or blue maculae on skin and oral mucosa [8]. Polyps may cause intussusceptions as an important clinical finding. A study by Boardman et al., reported that patients with Peutz-Jegher's Syndrome have 9.9 times increased risk for intestinal cancer compared to general population [9]. Thus, screening for intestinal cancer comprises an important part of management for these patients.

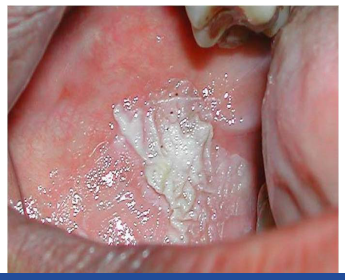
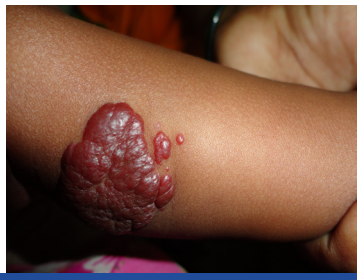
**Oral manifestations:** The brown pigmented macules are present at birth or usually noted at early childhood [8,10]. Pigmented lesions are seen on skin around the lips and the vermilion zone of the lips is a very common feature [11]. Intra orally, the lesions are usually brown pigmented, painless patches on the buccal mucosa, tongue or labial mucosa [12,13]. Microscopically, these lesions show mild acanthosis with elongation of rete pegs, and increased number of melanocytes and the adjacent keratinocytes filled with melanosomes [13].

**Molecular genetics:** The gene associated with Peutz-Jegher's Syndrome is LKB1/STK11 (serine/threonine-protein kinase 11,


**[Table/Fig-1]:** Scar producing bullae at elbow in epidermolysis bullosa. **[Table/Fig-2]:** Café-au-lait spots in von Recklinghausen disease. **[Table/Fig-3]:** Multiple neurofibromas hanging out of skin in von Recklinghausen disease.



**[Table/Fig-4]:** Conical shaped teeth in Gardner's syndrome.**[Table/Fig-5]:** Cutaneous pigmentations in dyskeratosis. **[Table/Fig-6]:** Leukoplakia on buccal mucosa in patient of dyskeratosis congenita. **[Table/Fig-7]:** Arteriovenous malformations in hemorrhagic telangiectasia.

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.

## Neurofibromatosis

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) [14,15].

NF1, also known as von Recklinghausen disease, is characterised by the presence of multiple café-au-lait spots [Table/Fig-2] defined as oval shaped light brown patches greater than 0.5cm in diameter, multiple cutaneous neurofibromas (tumours on, under, or hanging off the skin) [Table/Fig-3], axillary or inguinal freckling, Lisch nodules (tiny tumours on the iris of the eye) [15]. NF1 affects 1 in 3500 people worldwide [16].

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 [15]. NF2 are relatively infrequent. Tumours of the auditory nerves that lead to hearing loss, is usually the first symptom of the disease.

**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 [17]. 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 [18]. Superficial neurofibromas of tongue gives fissured (Scrotal) appearance, whereas the deep seated tumors gives an appearance of large tongue (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 [19].

**Molecular genetics:** Neurofibromatosis type 1 is a genetic condition caused by mutation on chromosome 17q11.2. The gene product being neurofibromin 1which activate ras-GTPase activating enzyme (GAP) expressed in cells and are involved in cellular signal transduction. Neurofibromatosis type 2 is caused due to mutation on chromosome 22q12.2, the gene 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) [21].

## MEN's Syndrome (MEN IIB)

Multiple endocrine neoplasia (MEN) syndromes are group rare auosomal 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 [22].

**Oral manifestations:** The oral submucosal 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 [22].

Mucosal neuromas may be found on the dorsal surface of tongue, palate, buccal mucosa and pharynx. The tongue neurofibromas appears crenated or notched [23]. 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 [23]. All of the findings in MEN IIB are generally thought of as asymptomatic and benign.

**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 [22].

## Cowden's Syndrome (Multiple Hamartoma Syndrome)

Cowden syndrome a rare genodermotosis 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 [24].

The hamartomas are characterised by mucocutaneous flat topped papules involving the oral, nasal, intestinal mucosa [23]. Patients with Cowden's syndrome have an increased risk of developing several types of cancer, including cancers of the breast, thyroid, and uterus [24]. Palmoplantar keratosis, vitiligo, neuromas, xanthomas and café au lait spots are additional skin findings reported infrequently association with Cowden's disease [25].

**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 [26]. The oropharynx, larynx and nasal mucosa may also be involved. The typical appearance of mulitiple, coalescent, flat topped mucosal papules has been described as cobblestone-like and is seen in 40% of patients [27].

**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 [28]. PTEN is a tumour suppressor gene, which helps to control the growth and division of cells is mutated leading to the formation of tumors.

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

Basal cell nevus syndrome 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 [29].

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, curvature of the back (scoliosis), severe curvature of the back (kyphosis) are seen. Other types of tumors can also occur in Gorlin syndrome, such as medulloblastoma (brain tumor) 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 [29].

**Molecular genetics:** The gene linked to the syndrome is PTCH1 gene localized to 9q22.3 [29]. 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.

## Gardener's syndrome (familial colorectal polyposis)

Gardner's syndrome 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 [30].

**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 [Table/Fig-4]. 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 [31].

**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 [32].

## Dyskeratosis congenita (x-linked recessive)

Dyskeratosis congenita can be characterized by classic triad of dystrophy of the nails, lacy reticular cutaneous pigmentation [Table/Fig-5] 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 [33].

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 [34].

**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 [Table/Fig-6], 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 [33,34].

**Molecular genetics:** Dyskeratosis congenita is characterized by X-linked recessive which is a result of one or more mutations in the long arm of the X chromosome in the gene DKC1. This results in the disease wherein the major protein affected is dyskerin [33]. The X-linked form of this disease may result in specific issues related to dysfunctional rRNA [35].

## Ehlers-Danlos Syndrome (Cutis hyperelastica)

It is a group of inherited disorders of connective tissue which supports the skin, bone, blood vessels and many other organs of the body. Ehlers- Danlos syndrome 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. There is no cure for the condition and treatment is mainly supportive, including close monitoring of the digestive, excretory and particularly the cardiovascular systems [36].

Ehler Danlos Syndrome (EDS) most 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. Early onset of osteoarthritis, easy bruising, dysautonomia (a disorder of the autonomic nervous system) 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 (womb) 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 [36].

**Oral manifestations:** The clinical manifestations of EDS in the orofacial region consist of extra-oral and intra-oral manifestations. Extra-oral manifestations consist of slender and asymmetric face, retrognathia, scars on the chin and forehead, repeated dislocations of TMJ, The area around the eye includes hypertelorism, epicanthus (a vertical fold of the skin on either side of the nose, sometimes covering the inner canthus), strabismus (abnormal alignment of eyes), narrow nasal bridge, shaggy hair, and sagging of the skin [37,38]. Moreover, intra-oral manifestations comprise high arched palate, crowding of teeth, highly fragile mucosa (similar to the patients' skin), which is easily ruptured when dental instruments touch them and sutures do not remain in place, usually bruising is evident on the oral mucosa [39].

**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 [37].

## Marfan's Syndrome

Marfan's syndrome is a heritable genetic disorder of the connective tissue. This syndrome is noted for its worldwide distribution, relatively high prevalence, and clinical variability involving ocular, skeletal, and cardiovascular systems, some of them is life threatening. People with Marfan's tend to be unusually tall, thin built with long limbs and long, thin spidery fingers. Spine curves on one side called scoliosis. The most serious complications are defects of the heart valves and aorta which includes aortic aueurysms and mitral valve prolapse and left ventricular dysfunction. Syndrome also affects the lungs, the eye, dural sac surrounding the spinal cord, the skeleton and the hard palate [40].

**Oral features:** Jaw bones present retrognathia, deep narrow palate leading to crowding of teeth. Angle's Class II molar relationship and lack of space for all of the dental structures which is caused by palatal position of upper laterals in relation to the centrals [40]. Root deformity, abnormal pulp shape, and pulpal inclusions were a frequent finding in patients with Marfans' syndrome [39]. Early diagnoses of both craniofacial and dental defects aid in early adequate treatment which in turn could definitely develop a satisfactory prognosis of these types of patients, considerably improving their quality of life.

**Molecular genetics:** The syndrome carried by the gene FBN1, which encodes the connective protein fibrillin-1 and is inherited as a dominant trait [41]. People have a pair of FBN1 genes [40]. This is mainly caused of mutations in the fibrilin glycoprotein's codified gene -1 located in the chromosome 15q21. Fibrillin-1 protein is essential for the proper formation of the extracellular matrix, including the biogenesis and maintenance of elastic fibers. The extracellular matrix is critical for both the structural integrity of connective tissue, but also serves as a reservoir for growth factors [41].

## Haemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

It is a rare autosomal dominant genetic disorder that leads to abnormal blood vessel formation which affects the skin, mucous membranes, and often organs such as the lungs, liver, spleen and brain, characterized by small and large arteriovenous malformations that become more prominent with age [Table/Fig-7]. Bleeding may cause sudden devastating consequences.

**Oral manifestations:** Oral lesions may be punctate, spider like or nodular and be found on buccal mucosa, tongue, lips, palate and gingiva [42]. Colour may vary from bright red to purple but in oral mucosa usually cherry red.

**Molecular genetics:** Two main genetic subtypes of Haemorrhagic Telangiectasia (HHT) have been described HHT1 and HHT2. Mutations most commonly involve the endoglin gene (ENG) on chromosome 9q34.1 for HHT1or the Activin receptor Like Kinase Type I (ALK-1) gene on chromosome 12q1for HHT2. Both ENG and ALK-1 encode putative receptors for the transforming growth factor-beta (TGF-β) superfamily that plays a critical role for the proper development of the blood vessels [42].

**Prenatal Diagnosis (PND), Genetic counselling and Treatment:** PreNatal Diagnosis (PND) may be chosen to assess the high risk for severe cases of genodermatoses. Estimation of genetic risk should be highly accurate. Genodermatoses are monogenic diseases inherited as Mendel's law of segregations and genetic risk can be estimated mathematically as a probability of severe genetic abnormality.

Genetic counselling is the process of advice where the patient or family are given information on the type of inheritance, risk of occurrence, prognosis of a disease, prevention and treatment. Genetic counselling should be carefully done for patients and their families and they should be provided with accurate information on the diseases based on the ethical considerations. PND in genodermatoses is performed mainly by villus sampling (At 10$^{th}$ week of pregnancy, foetal placental villi are collected) and foetal tissue biopsy (At 19$^{th}$ week of pregnancy, fetus skin biopsy taken by using ultrasound). The diagnosis genetic disease is determined by extraction of fetal DNA by direct sequencing of fetal DNA, restriction enzyme digestion, and allele-specific oligonucleotide hybridization [43].

There are no specific effective treatments for genodermatoses. Causative genes are identified and are targeted by gene replacement therapy and gene expression inhibition therapy. Studies are being done to transplant the patient's cultured cells which have normal genes directly to the patient's skin or mucosa. Recently allogenic bone marrow transplantation, in which bone marrow stem cells are differentiated to epidermal stem cells to cure genodermatoses is being tried [44].

# CONCLUSION

There is now better understanding of the genetic basis of oral genodermatosis and significant progress owing to the advent of

novel molecular biological technologies and major developments in computational methods. Knowledge of the genetic basis of these conditions helps in determining the gene function and its correlation to its genotype with phenotype [summary of oral genodermatoses with their causal gene/protein [Table/Fig-8]. Mutational analysis not only helps in genetic counselling and to make DNA-based prenatal diagnosis in high risk families, it is also useful in developing the targeted therapeutic options.

The lack of awareness and rarity of these disease conditions are the major drawback in diagnosing and management. Unlike the developed countries, India lacks the multi-speciality or multi-centric network to share the information on these conditions. So, oral genodermatosis registry should be initiated to know the incidence and to develop novel preventive and therapeutic tools.

| Genodermatoses with oral manifestations | Causal protein/gene |
|---|---|
| Dystrophic Epidermolysis Bullosa | Type VII collagen |
| Peutz-Jeghers Syndrome | STK11/LKB1 |
| Neurofibromatosis | NF1 & NF2 |
| MEN Syndrome | RET gene for MEN IIB |
| Cowden Syndrome | PTEN |
| Gardner's Syndrome | APC |
| Basal | Cell Nevus Syndrome |
| Dyskeratosis Congenita(x-linked recessive) | DKC1 |
| Marfan's Syndrome | Fibrilin-1 |
| Haemorrhagic Telangiectasia | Endoglin And Activin Receptor Gene |

**[Table/Fig-8]:** List of Genodermatoses with oral manifestations and their causal protein/gene

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