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## Oral Disorders Attributed to Genetic Variants : Pathogenesis and Treatment

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## Oral Disorders Attributed to Genetic Variants : Pathogenesis and Treatment

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# Genetically Caused Oral Disorders: Pathogenesis and Treatment: A review

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## Abstract

**Background:** The mouth is a unique and intricate structure composed of various anatomical components that work together effectively to perform various functions. The oral cavity can be affected by various disorders, such as genetic diseases, infections, and metabolic disorders.

A wide range of genetic disorders can affect the skeletal system, including craniofacial structures and teeth. These disorders exhibit a significant variety in terms of their causes when they show up, and how severe they are. Genetics is a significant risk factor in the development of oral diseases. It affects the pattern of inheritance, which can be dominant, recessive, or both. The transmission of genetic variation from one generation to the next is a significant contributor to the development of various diseases, having both direct and indirect impacts.

**Objective:** Our study seeks to shed light on the genetic causes and symptoms of diseases that affect bone and mucosal tissues. We will also investigate the associated symptoms and explore the various diagnostic and treatment options available for these specific genetic disorders.

**Conclusion:** The scientific study of oral genetic disorders is still in its early stages, and further research is necessary to improve diagnostic, prognostic, and treatment methods.

**Keywords:** Genetic disorders, Genetic causes, Symptoms, Diagnostics and treatment, Human genetic

## Introduction

Hereditary disorders impacting the skeletal system, encompassing the craniofacial and dental structures, display notable heterogeneity concerning their etiology, onset, and severity. Despite advancements in comprehending the underlying causative factors, pathologies, and mechanisms of bone diseases, those affecting the dental-oral-craniofacial (DOC) complex often remain understudied. This oversight bears substantial implications for diagnosing and treating affected individuals, thereby influencing their overall well-being and quality of life. Simultaneously, oral mucosal diseases, prevalent within the general populace, present diverse clinical manifestations, affecting general population life qualities and underscoring the significance of identifying associated risk factors (Foster et al., 2014; Stoopler &

Sollecito, 2014). One of the major risk factors involved in the pathogenesis of oral diseases is genetics, which plays a role in several ways, including the pattern of inheritance (Inheriting a complete set of genes from each parent in different modes of inheritance, either dominant, recessive, or both). The transmission of genetic variation from one generation to successive generations plays a substantial role in the etiology of diverse diseases, exerting direct and indirect influences (Blazer & Hernandez, 2006).

Genetic disorders affecting both the bone and mucosal tissues can give rise to a diverse range of symptoms. In terms of bone diseases, direct genetic influences may contribute to conditions like malocclusion, one of the most prevalent oral pathologies characterized by misalignment of the teeth and jaws, leading to functional and aesthetic issues (Agarwal et al., 2015). Additional symptoms

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associated with oral bone deformities include jaw pain, difficulty or discomfort in jaw movement, jaw clicking or popping, jaw swelling or inflammation, facial asymmetry, and difficulties with chewing or biting.

On the other hand, genetic influences on mucosal tissues can result in various conditions, such as Recurrent Aphthous Stomatitis (RAS) and White Sponge Nevus (WSN), which can lead to symptoms that significantly impact a person's appearance and ability to eat, drink, and speak. These symptoms may include alterations in color, pain, variations in surface characteristics, swelling, the presence of sores or patches, burning or scalding sensations, and itching or tingling sensations in the mouth (López-Jornet et al., 2009).

By understanding the diverse manifestations of these direct genetic influences on both bone and mucosal tissues, researchers and healthcare professionals can improve diagnosis, develop targeted treatments, and enhance the overall management of individuals affected by these genetic disorders (Table 1).

The present study aims to illuminate the genetic underpinnings and accompanying symptoms of genetic diseases affecting the bone and mucosal tissues, explore their associated symptoms, and examine diagnostic and treatment modalities employed for these specific genetic disorders.

Table 1. Some genetic diseases of bone and mucosa.

Bone	Mucosa
<ul style="list-style-type: none"> <li>• Mandibular Prognathism</li> <li>• Mandibular retrognathism</li> <li>• Cherubism</li> <li>• Hypophosphatasia</li> </ul>	<ul style="list-style-type: none"> <li>• Recurrent aphthous stomatitis</li> <li>• White sponge nevus</li> </ul>

## Mandibular prognathism (MP)

### History

An abnormal forward protrusion of the mandible beyond its normal relationship to the cranial base (Fig. 1), is referred to as mandibular prognathism (MP) (Doraczynska-Kowalik et al., 2017) (taken from the Greek pro-forward and gnathos = jaw) (Ngan et al., 2014). The cause of mandibular prognathism is uncertain, but various genetic, epigenetic, and environmental factors may be involved (Doraczynska-Kowalik et al., 2017). According to studies on family aggregation, heredity is a major factor. Interestingly, they discovered no significant gender differences (Otero et al., 2014).

Angle defined class III malocclusion in the early 1900s as the mandibular first permanent molar being “mesial,” or forward to normal, in its relationship with the maxillary first molar. Lischer later referred to this condition as mesio-occlusion. This classification method, however, does not provide information about the developmental mechanisms that led to the observed occlusal relationship (Angle, 1907; Chang et al., 2006).

Further research revealed that the first molar occlusion is not the cause of more than 60% of prognathism but rather an imbalance in the growth of the upper and lower jaws (Zahro et al., 2022).

Charles Henry Tweed described two types of Class III malocclusions: pseudo-class III malocclusion with an underdeveloped maxilla and a normal mandible, and skeletal Class III malocclusion with an underdeveloped maxilla and a prognathic mandible (Zere et al., 2018). The prevalence of mandibular prognathism differs between ethnic groups (Chang et al., 2006).

It is worth mentioning that many studies have been conducted to assess this condition's effects on adolescents' quality of life and have revealed that it is associated with a higher level of dissatisfaction with facial appearance (Rezaei et al., 2019).

### Genetic causes

The genes MATN1, EPB41, ADAMTS1, ARH-GAP21, COL2A1, MYO1H, and SMAD6 have been proven to be closely associated with MP (Jaruga et al., 2022), whereas the gene of growth hormone receptor (GHR) has been disputed (Liu et al., 2017), but a recent study supports the possibility that the growth hormone receptor (GHR) is susceptible to mandibular morphogenesis (Park et al., 2022). Furthermore, the roles of genes BMP3, ANXA2, FLNB, and HOXA2 require further investigation due to the high risk of information bias (Liu et al., 2017).

### Symptoms

Individuals with MP have a concave facial profile. These clinical characteristics are primarily the result of the mandible's extreme forward growth (Zahro et al., 2022). Furthermore, Long Face Syndrome, a manifestation of the class III malocclusion phenotype, can occasionally occur.

Patients mostly have aesthetic issues as well as a vertical functional pattern, which limits function to vertical movements. Class III malocclusion is frequently associated with complex dentoalveolar problems such as tooth edge-to-edge position or

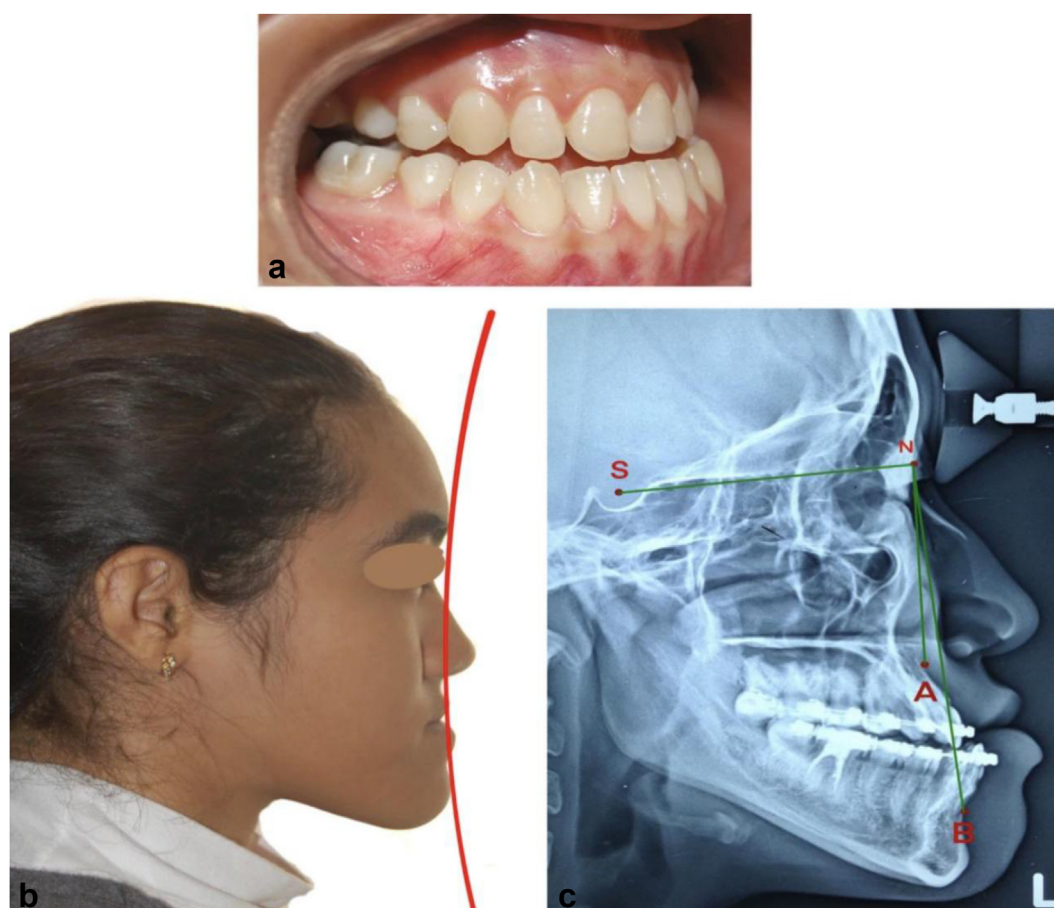


Fig. 1. Mandibular Prognathism (MP), a) Intraoral side, b) The profile of the face is concave, and the chin appears to be protruding, c) Cephalometric analysis. Copyright. Egyptian Journal of Medical Human Genetics. Ref. Laviana et al., 2021.

posterior cross-bite (Mousoule et al., 2016). In addition to difficulties with speech, chewing (Laufer et al., 1976), and mouth breathing (Martinelli et al., 2011).

In several cases, there is a clear disruption in the interaction between the upper and lower lips, and there may be signs of upper lip atrophy, lower lip eversion, problems making good contact, or even a loss of connection between them (Jaruga et al., 2022; Liu et al., 2017).

#### Diagnostics and treatment

It is widely accepted that skeletal Class III malocclusion, which develops early in life, is not a self-correcting disharmony. According to several studies, treatment should be administered to patients who are under 10 years old. However, several investigations revealed that the patient's age had little bearing on how they responded to treatment and how well they did. The idea that early therapy would be advantageous is not strongly supported by

the available research. Early intervention primarily aims to enhance the occlusal connection and provide a more favorable environment for growth. Interceptive treatment of Class III malocclusions is permissible if it prevents tissue damage and/or significantly reduces the amount or severity of future orthodontic treatment (Zere et al., 2018). In the past, one of several approaches has been used to treat this condition. The chin cup has been used in growing patients to restrain or change the direction of mandibular growth, and the facemask has been used to protract the maxilla for orthopedic correction. The optimal time to use a facemask for interceptive treatment is during the deciduous or early mixed dentition stage. Patients should be advised to wear the chin cup appliance after facemask therapy until their growth is complete. Although these appliances can correct a Class III incisor relationship, any orthopedic changes are likely to be minimal. Simple anterior dental crossbites in mixed dentition can be successfully corrected with removable or fixed appliances (Moon & Khullar, 2014).



Surgical orthodontic treatment of prognathism patients traditionally includes presurgical orthodontic treatment for tooth position decompensation caused by undesirable jaw growth, followed by surgical correction of the skeletal discrepancy and postsurgical detailing and finishing of the occlusion (Kee et al., 2023). Adult MP patients must be corrected with orthognathic surgery and orthodontic treatment. It takes between 9 and 12 months to fully recover from orthognathic surgery. Sagittal split ramus osteotomy (SSRO) and intraoral vertical ramus osteotomy (IVRO) are the two most commonly used surgical procedures to correct MP (Chang et al., 2006).

### Mandibular retrognathism (MR)

#### History

Mandibular retrognathism is a common oral and maxillofacial deformity that can lead to many physical and psychological problems (Wang et al., 2020). Is a form of malocclusion that describes the mandible being abnormally positioned posteriorly as a result of a developmental anomaly (Fig. 2). The term retrognathism comes from the Latin retro, which means “backward”, and from the Greek gnathos, “jaw” (Cascarini, 2007).

Edward Angle, widely regarded as the father of orthodontics, invented a classification system for the occlusion of teeth and how they relate to one another

(Okeson, 2015). On average, the prevalence of Class II is around 27% (Lone et al., 2023). These skeletal malocclusions are thought to be caused by a combination of general and local factors, with general factors including genetic and hereditary etiology, environmental factors, and traumatic injuries, and local factors including tooth shape, size, and number (Ardani et al., 2020). Several studies have found that genetic factors play a significant role in the development of mandibular retrognathism (Wang et al., 2020). Retrognathia is a condition in which the lower jaw is out of place in relation to the upper jaw. Micrognathia, on the other hand, is characterized by a smaller-than-normal jaw. Clinical manifestations are frequently very similar (Sanz-Corté et al., 2018). Class II is further subdivided into two parts: Division 1: The anterior maxillary teeth are proclined forward, resulting in a large overjet. Division 2: The anterior maxillary teeth are retroclined, resulting in a significant overbite (Barber et al., 2015).

#### Genetic causes

The genes FGFR2, MSX1, ACTN3, GHR, KAT6B, HDAC4, and AJUBA have been linked to skeletal class II malocclusion, In addition to MATN1 and MYO1H (George et al., 2021). Most families that have been documented to date have undergone genetic testing that has uncovered eight possibly novel genes (GLUD2, ADGRG4, ARSH, TGIF1, FGFR3, ZNF181, INTS7, and WNT6). A discovery in



Fig. 2. Presents photographs capturing the severe mandibular retrognathism and bilateral condylar deformities in a patient, which became evident post the completion of growth. Ref. Nakamura et al., 2016.

mandibular genetics that had not previously been seen (El Chekie et al., 2022). Some findings suggest the etiology of human mandibular retrognathism (MR). Maybe related to single nucleotide polymorphisms (SNPs) in the parathyroid hormone (PTH), vitamin D receptor (VDR), CYP24A1, and CYP27B1 genes involved in the maintenance of vitamin D levels (Gershater et al., 2021). Also, one of the studies reports a link between the COL2A1 SNP and mandibular retrognathism (Kalmari et al., 2022).

### *Symptoms*

Patients with retrognathism have a maxilla that is anterior to the mandible, which could be due to inadequate lower jaw growth and size and/or excessive upper jaw growth and size (Ngan et al., 1997). Class II skeletal malocclusion is distinguished by skeletal dissonance, which usually causes a decreased chin projection and a convex facial profile. Furthermore, due to other common features such as projecting upper incisors, a decreased mento-labial angle, a retruded lower lip, and a short chin-throat distance, the subject's facial attractiveness may be diminished (Santori et al., 2021). Skeletal class II impairs patients' ability to chew food effectively (Bae et al., 2017). Moreover, this condition has been associated with temporomandibular disorder (TMD), periodontal disease, and dental decay; this prevalence is especially high among children in Southern Italy, according to several studies (Perrotta et al., 2019), as well as other parts of the body, such as myofascial pain (de Paiva Bertoli et al., 2018).

### *Diagnostics and treatment*

The majority of orthodontic and facial orthopedic treatment procedures used to correct Class II malocclusions are limited to modifying maxillary incisor prominence through tooth retraction and downward redirection of maxillary growth (McNeill & West, 1977).

Are known to be visually unappealing traits from a cosmetic standpoint, which may also harm patients' psychological well-being and decrease their perception of their own worth. Conversely, the surgical correction could significantly boost their self-esteem and reduce their concerns about their physical appearance. As a result, facial attractiveness, along with correct dental occlusion and functional equilibrium, should be one of the treatment goals for Class II skeletal malocclusion (Santori et al., 2021).

For severe skeletal class II malocclusions, orthognathic surgical treatment is still utilized as a

last option. However, because it is an invasive treatment, orthognathic surgery has several dangers, some of which are serious, including decreased feeling, infection, hemorrhage, tissue damage, and adjustments to the osteosynthesis systems. More crucially, in order to make the correct diagnosis and prevent subsequent procedures to address malocclusion recurrence brought on by post-surgery growth, the majority of orthognathic surgeries can only be carried out when individuals are skeletally mature (Gershater et al., 2021). Several studies have shown that orthodontic-surgical treatment is more effective for the ANB, SNB, and ML/NSL angles, as well as the soft tissue profile, including the nose (Ló et al., 2022).

Several treatment options for the correction of dental and skeletal Class II malocclusion in growing patients have been described in the literature, including a two-stage treatment using a functional appliance in the first stage and a fixed appliance in the second; either a one-stage treatment that combines an extraoral appliance with a fixed device; or using mandibular fixed protraction equipment, such as Herbst and Forsus, prior to or concurrently with a fixed appliance. Recently developed Align Technology has a “wings” system for its aligners to correct Class II malocclusion through mandibular protraction. However, there is no scientific evidence to support this system (Rédua, 2020).

## **Cherubism**

### *History*

Cherubism, or multilocular cystic disease of the jaws, is a congenital childhood disease of autosomal dominant inheritance (Figs. 3–5). This disease is distinguished by painless swelling of the jaws and bone replacement with fibrous tissue. The condition has unique clinical, radiographic, and histological features. In 1933, W.A. Jones, J. Grieve, and J. Pritchard originally identified it as a distinct entity in a family with many sick individuals. To express how “the full round cheeks and the upward cast of the eyes give the children a peculiarly” cherubic appearance, he coined the word “cherubism” (Jones et al., 1950; Papadaki et al., 2012). It's widely recognized as a classic familial condition, with a strong tendency for inheritance patterns to be present in documented cases more frequently than non-familial ones. The rarity of the disorder makes it difficult to determine its true prevalence, although it has been demonstrated that men and women of all racial and ethnic backgrounds experience cherubism equally (Papadaki et al., 2012).

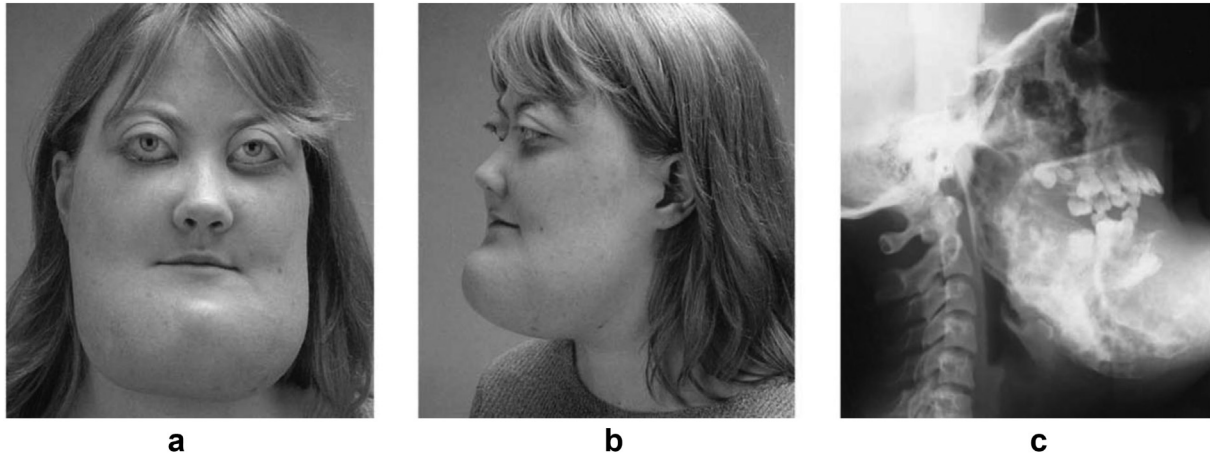


Fig. 3. Photographs and an x-ray showing the condition of a 19-year-old girl with cherubism, who belongs to family CH1 a) Characteristic facial disfigurement of cherubism is shown in the anterior-posterior view. The overgrowth of maxilla causes visible sclera below iris, b) This lateral view highlights the mandible that protrudes and the eyes that are pushed forward. c) The X-ray shows that the pathology is limited to the skull bones formed by endochondral ossification. Copyright The American Journal of Human Genetics. Ref. [Mangion et al., 1999](#).

#### Genetic causes

The main cause of Cherubism is the mutation in the SH3BP2 gene (SH3-binding protein 2), which is found on chromosome 4p16.3, and Cherubism-related mutations in exons 3, 4, and 9. Exon 9 of the

SH3BP2 gene, where a single nucleotide substitution causes a missense point mutation, has been proposed as the host site for cherubism disease, while exon 3 is observed in severe cherubism. ([Reichenberger et al., 2012](#)). A mutation in the FGFR3 gene (the gene for fibroblast growth factor receptor 3) was

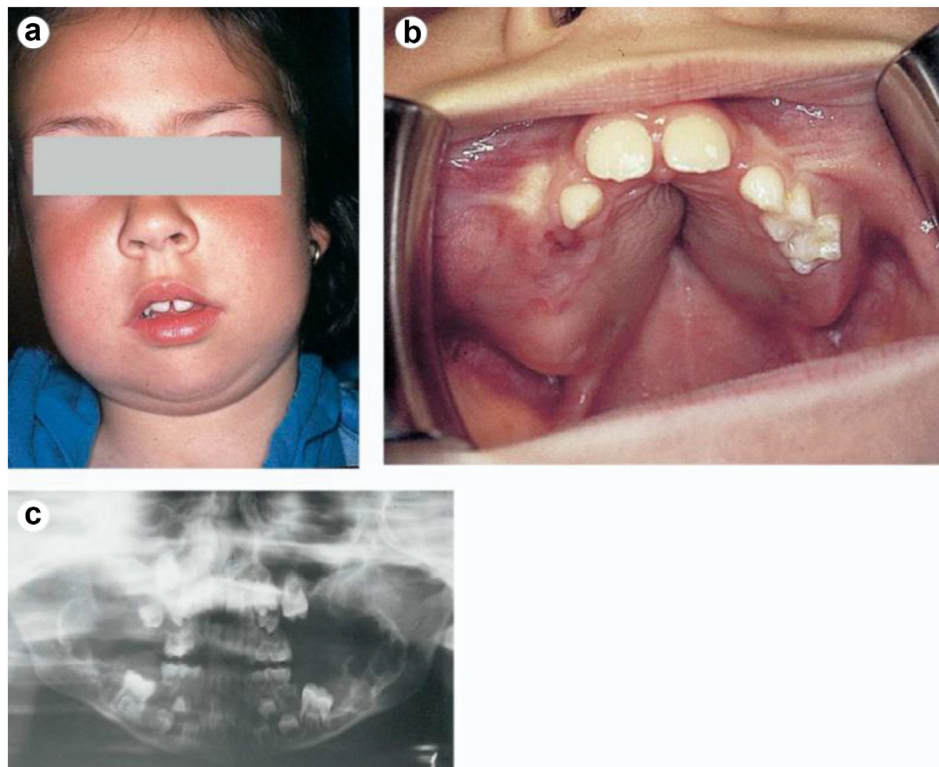


Fig. 4. Photographs and an x-ray showing patients diagnosed with cherubism a) the patient's facial appearance displays bilateral swelling of the mandibular angles b) an intraoral image displays the thickening of the alveolar processes and partial obliteration of the palatal vault c) the panoramic radiograph displays clearly defined, multilocular radiotransparencies in both the maxillary and mandibular regions. Copyright Journal of oral and maxillofacial surgery. Ref. [Peñarrocha et al., 2006](#).



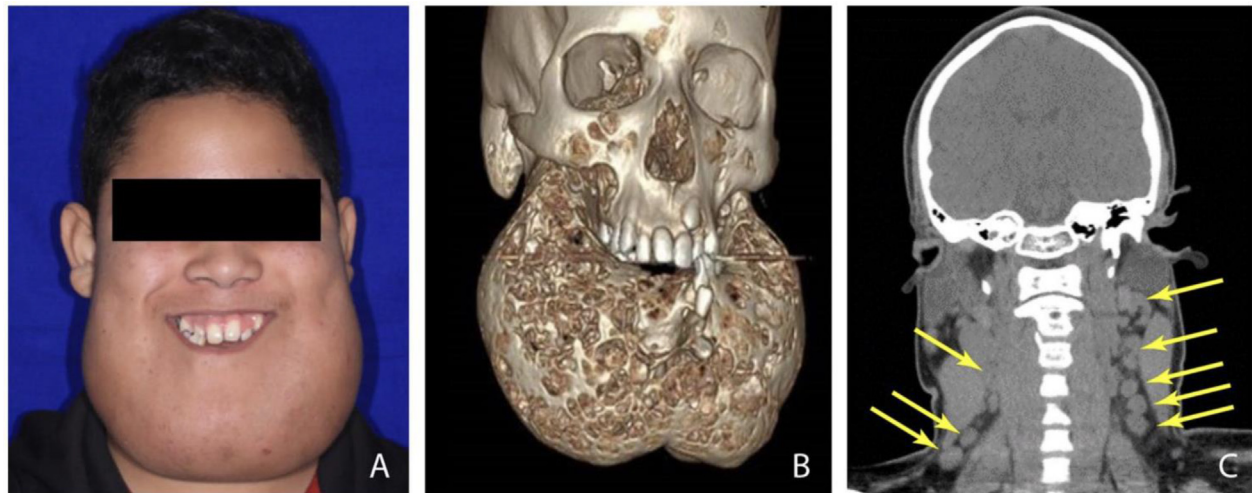


Fig. 5. A 14-year-old boy exhibited bilateral enlargement of the mandible, which was impacting both his speech and ability to chew. This enlargement persisted without subsequent reduction (A). CT scans revealed extensive osseous restructuring characterized by a multilocular appearance and a coarse trabecular pattern in the mandible. There was also noticeable dental misalignment specific to the mandible, with no signs of orbital or definitive maxillary involvement (B). The CT images additionally highlighted numerous enlarged lymph nodes in the regional vicinity (indicated by the arrow) (C). "CT" stands for computed tomography. Ref. [Chen Wongworawat et al., 2019](#).

suspected of being associated with Cherubism ([Mangion et al., 1999](#)), but according to the most recent studies on the subject, the researchers excluded it ([Stiller et al., 2000](#)).

#### Symptoms

The phenotype can range from no clinical manifestations to severe symmetrical mandibular and maxillary overgrowth, which gives the cheeks a swollen appearance. Other symptoms have been found in Problems with speech, mastication, and swallowing ([Kannu et al., 2007](#)). Upper airway obstruction can be caused by backward displacement of the tongue ([Ladhani et al., 2003](#)), or obliteration of the nasal airway can occur on occasion. These results may result in mouth breathing, snoring, chronic nasal infections, and obstructive sleep apnea ([Battaglia et al., 2000](#)). Symptoms like orbital manifestations, including proptosis, visual loss due to displacement and atrophy of the optic nerves, diplopia, physical displacement of the globe, and retraction of the eyelids, may also be present, and the disease may invade the retrobulbar spaces of the orbits ([Carroll & Sullivan, 2001](#); [Timoş et al., 2000](#)). The majority of patients exhibit various dental abnormalities such as displaced, unerupted, or unformed teeth and the presence of teeth that appear to be floating in cyst-like spaces; this is in addition to malocclusion, expansion of the alveolar ridges, premature exfoliation of deciduous teeth, and root resorption ([Kannu et al., 2007](#); [Motamedi, 1998](#)).

#### Diagnostics and treatment

Doctors cannot diagnose cherubism at birth because symptoms do not appear. Later, they conduct a physical exam, X-rays, and a CT (computed tomography) scan to diagnose the condition. In addition, review the family history for signs of an inherited disease ([Weishaupt, 2021](#)). Although the disease primarily necessitates maxillofacial surgery and orthodontic care, patients must also be consulted by an ophthalmologist ([Carroll & Sullivan, 2001](#)). After diagnosis, therapeutic management is assessed. Options for treatment include waiting for stabilization and spontaneous remission of the disease, tooth extraction in areas showing fibrous alterations, cosmetic osteoplasty of the affected jaws after regression of disease activity, or if there is functional impairment, curing the lesions, and treatment with calcitonin ([de Lange et al., 2007](#); [Raposo-Amaral et al., 2007](#)). The most advised treatment is to wait for disease regression; however, it is still uncertain ([Kaugars et al., 1992](#); [Kozakiewicz et al., 2001](#)).

Early surgical intervention with curettage and osteotomy followed by bony repositioning can be considered for the management of moderate to severe cases of cherubism, as it is a relatively minimally invasive and safe technique. When performing osteotomies, the piezoelectric bone cutter allows for a safer approach to the surrounding soft tissue. Curettage of the tumor restores mandibular anatomy without causing any damage to the teeth, arteries, nerves, or buccal soft tissue ([Moss et al., 2022](#)).

Human monoclonal antibody Denosumab Therapy in Cherubism, which binds to RANKL (receptor activator of nuclear factor kappa beta NFkB ligand) and suppresses osteoclasts to minimize bone resorption, can be advantageous for inhibiting bone growth to lessen the need for surgery and to manage postoperative proliferation. Close observation is necessary to maintain adequate electrolyte levels (Kawamura et al., 2020; Liles et al., 2022).

## Hypophosphatasia (HPP)

### History

Hypophosphatasia, also called Rathbun's syndrome and sometimes abbreviated HPP, is a deficiency of alkaline phosphatase that leads to the accumulation of several compounds, including phosphoethanolamine (PEA), in the body (Salles, 2020).

It is an inherited metabolic disorder characterized by defective mineralization of bones and teeth, with a wide variety of manifestations. The Inheritance of perinatal and infantile hypophosphatasia commonly appears in an autosomal recessive pattern. However, milder types, including adult and odonto-HPP, might have been inherited in an autosomal recessive or autosomal dominant manner.

In classifications of genetic conditions, Hypophosphatasia may be categorized as metabolic bone disease, skeletal dysplasia, metaphyseal dysplasia, dental condition, or disorder of membrane-bound ectoenzyme activity in the extracellular matrix (Nunes, 2007).

Hypophosphatasia (HPP) was first reported by John Campbell Rathbun in 1948; he also coined the term “hypophosphatasia” (Rathbun, 1948). Although Rathbun is rightly given credit for establishing the syndrome as an entity, Dr. Bruce Chown (Chown, 1936) published a paper in 1936 that described cases that are now recognized as consistent with hypophosphatasia.

HPP is distributed worldwide, although with a very variable incidence rate.

The prevalence of moderate HPP in a European population was approximately estimated to be 1/6370 (Berkseth et al., 2013), whereas the prevalence of severe HPP is 1/300,000. Mild forms are present, with an estimated prevalence of 1/508, indicating that mild forms of the disease likely occur more frequently (Mornet et al., 2021).

### Genetic causes

Mutations in the ALPL gene, also named the TNSALP gene, which is localized in chromosome

1p36.1–34, are responsible for Hypophosphatasia HPP disease (Mornet, 2000), which will make HPP patients have an inactive TNSALP (tissue-nonspecific alkaline phosphatase) enzyme; therefore, inorganic pyrophosphate is not degraded and phosphate will not be able to bind, and bone mineralization is impaired because of the disruption of hydroxyapatite development and formation (Okawa & Nakano, 2022). Therefore, hypophosphatasia is a result of a lack of bone mineralization rather than inadequate bone mineralization because the bone mineralization process is not functioning properly, as mentioned earlier. Over 340 mutations have been reported to be responsible for HPP; these mutations include missense mutations, nonsense mutations, small insertions, small deletions, large deletions, and complex deletions and insertions (Mornet, 2018).

### Symptoms

The symptoms of HPP are highly variable, from the most severe forms to the mildest forms, typically inversely proportional to the age at the onset of the initial symptoms (except for perinatal benign HPP), and at any age, new symptoms can manifest; they can also get worse over time, leading to serious disability (Bloch- and Zupan, 2016). The disease is usually classified into six clinical disease forms (Michigami et al., 2020; Villa-Suá et al., 2021), which are:

- (1) Perinatal Hypophosphatasia: The most severe subtype, perinatal fatal HPP, manifests in utero or at birth with an almost complete lack of bone mineralization and can result in fetal death. Short-limbed dwarfism, bowed bones, skin-covered osteochondral spurs protruding from the legs or arms (a pathognomonic trait), hypoplastic lungs, and defective skull and spine mineralization are all radiographic findings that are highly indicative of the disease.
- (2) In the “benign perinatal” form, extremities' bones exhibit poor mineralization symptoms during a gestational ultrasound. These individuals have limb shortening and bending, as well as dimples that mask lengthy bone abnormalities.
- (3) Infantile Hypophosphatasia clinical manifestations occur during the first 6 months of age. Craniosynostosis is a manifestation that may appear in infantile HPP and can cause intracranial hypertension, papilloma, or plagiocephaly. On the other hand, a wide fontanelle that slowly

closes, metaphyseal abnormalities, shaft invasion, and very fragile bones could also appear. Other manifestations could be proptosis, mild hypertelorism, and brachycephaly.

- (4) Childhood-onset HPP is diagnosed after six months. However, it is important to note that the onset of symptoms is not the same as the age of onset of the condition. In some cases, the signs and symptoms of hypophosphatasia may not become apparent until later in childhood or even adulthood. Bone abnormalities may be modest, and the condition may merely result in the early loss of primary teeth (incisors frequently first); nonetheless, it is linked with moderate HPP-related rickets, short stature, delayed walking or gait deficits, and pain in the lower limbs in certain cases.
- (5) Adult HPP generally emerges in middle age, even though there is usually a history of premature primary tooth loss. It is characterized by early permanent tooth loss, which is frequently linked with numerous fractures, including osteomalacia, chondrocalcinosis, osteoarthropathy, and stress fractures. Some occurrences are linked to a familial or personal history of moderate rickets during childhood.
- (6) Odontohypophosphatasia exclusively manifests in the mouth and can develop at any age. There is alveolar bone loss, but no other skeletal abnormalities are identifiable. Dental features include early dental exfoliation (incisors), reduced thickness of the dentin, enlarged pulp chambers of teeth, and dental caries.

#### *Diagnostics and treatment*

HPP can be diagnosed in utero, in youth, and in adulthood. Overall, the most severe types of the disease have earlier symptoms and diagnoses. Milder types of the disease are typically identified later in life (Linglart & Biosse-Duplan, 2016). Though HPP is diagnosed based on clinical symptoms, radiographic findings, and biochemical test results, it must be distinguished from other bone disorders such as rickets, osteomalacia, and osteogenesis imperfecta. ALPL gene testing is advised for a definite diagnosis (Okawa & Nakano, 2022). Supportive treatment is important for HPP patients, including mechanical ventilation, accurate fracture treatment, physical therapy, dental monitoring, and follow-up care to avoid subsequent problems. A causal Enzyme Replacement Therapy (ERT) with asfotase-alfa was approved by the Food and Drug Administration (FDA) in 2015 to treat perinatal, infantile, and juvenile-onset HPP (LaSalle, 2017).

Asfotase-alfa improves respiratory insufficiency, bone mineralization, and long-term survival and has a very good safety profile (Whyte et al., 2016). Though initiating ERT therapy at an early stage of life may be crucial to avoid deciduous tooth exfoliation (Takagi et al., 2020).

### **Recurrent aphthous stomatitis (RAS)**

#### *History*

Recurrent aphthous stomatitis (RAS), also referred to as painful oral Aphthous ulcers or canker sores, is a chronic inflammatory disease of the oral mucosa. The term “aphthous” originated from the Greek word “aphthi”, which means “to inflame” Figs. 6 and 7. RAS is one of the most common oral mucosal disorders; it is characterized by round or ovoid painful ulcers that recur on the oral mucosa (Edgar et al., 2017). Johann von Mikulicz-Radecki, a superb surgeon of Polish origin, first described the condition in 1898. To honor the author, aphthae are traditionally referred to as Mikulicz's aphthae (von Mikulicz-Radecki et al., 1922; Kuczkowski et al., 2004). The etiology of recurrent oral ulcerations has been linked to local trauma, hereditary factors, dietary inadequacies, viral and bacterial infections, and immunological or endocrine disorders (Edgar et al., 2017). RAS estimated prevalence ranges from 5% to 20% of the general population (Ślebioda et al., 2013), although prevalence may vary from 5% to 60% depending on the study, the population assessed, the diagnostic criteria applied, and environmental factors (Jurge et al., 2006). The peak age for the onset of RAS is in the range of 10–19 years. Although the condition is less common in adults, it can last for the rest of a person's life (Ship et al., 2000). Some research papers reported equal effects on both females and males of this disease, while females tend to be at higher risk of developing it than males (Ślebioda et al., 2013; McCullough et al., 2007). It has been shown that 24%–46% of RAS patients had a hereditary predisposition to develop an aphthous ulcer (Rogers, , 1997; Scully & Porter, 2008). The inheritance of RAS appears in an autosomal recessive pattern (Ślebioda et al., 2013). Cooke (1969) classified the lesions of RAS into three groups, and Lehner (1968) characterized them from a study of 210 patients. Considering the clinical features, three main types of recurrent aphthous stomatitis can be defined: Minor aphthae (most common), representing 70%–85% of all RAS patients, are also referred to as Mikulicz's aphthae (MiRAS), major aphthae (Sutton's aphthae; MaRAS), which are less common with a rate of 7%–



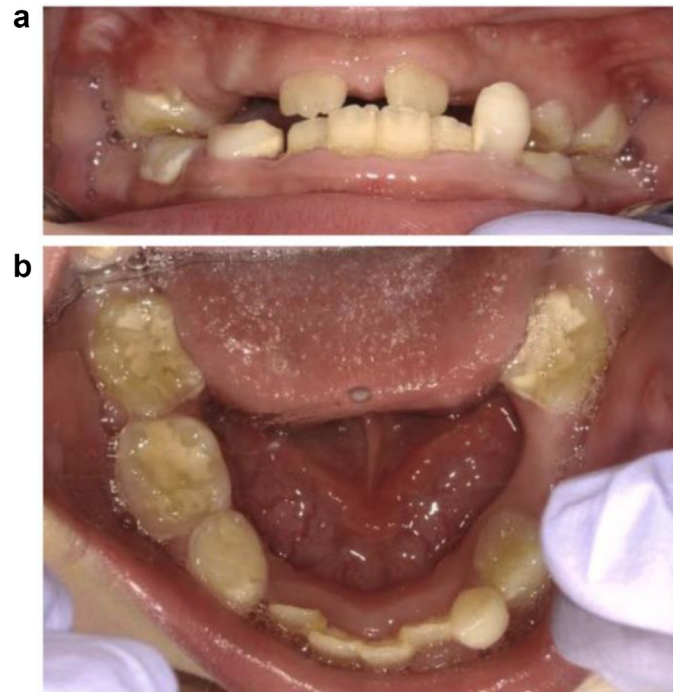


Fig. 6. Intraoral images depict an 8-year and a 10-month-old girl diagnosed with perinatal HPP. The photographs reveal noticeable enamel hypomineralization and multiple occlusal challenges, including mandibular prognathism, crowding, deep bite, a high-arched palate, and a V-shaped arch of the maxilla. Ref. [Okawa and Nakano, 2022](#).

20% of the cases, and herpetiform aphthae (HeRAS), which are rare and present as groups of pinpoint ulcers in 5%–10% of RAS ([Ślebioda et al., 2013](#); [Queiroz et al., 2018](#)). RAS may be associated with other systemic disorders, including Ulcus vulvae acutum, behçet's disease, MAGIC syndrome, FAPA syndrome, cyclic Neutropenia, aphthous-like ulcerations of HIV disease, and hematinic deficiencies Celiac Disease (sprue, gluten-sensitive enteropathy), Inflammatory bowel disease ([Rogers, , 1997](#)).

#### Genetic causes

Research has shown that alterations in the metabolism of cytokines, including interleukins (IL-1B, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, and IL-13), interferon  $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), serotonin

transporter gene (SLC6A4), and endothelial nitric oxide synthase gene (NOS3) ([Ślebioda et al., 2013](#); [Guimarã et al., 2007](#); [Ślebioda et al., 2014](#)), are associated with recurrent aphthous stomatitis (RAS). However, the exact mechanisms by which NOS3 (eNOS) gene polymorphisms contribute to the development of RAS are not fully understood and require further investigation, such as identifying potential genetic or environmental risk factors that interact with NOS3 gene polymorphisms to increase the risk of RAS or investigating the molecular mechanisms by which NOS3 gene polymorphisms affect nitric oxide production and activity in the oral mucosa. Researchers have also linked TGF- $\beta$ 1 gene to an increased risk of recurrent aphthous stomatitis (RAS) ([Kounoupis et al., 2022](#)). Compared to healthy controls, RAS patients have higher rates of the

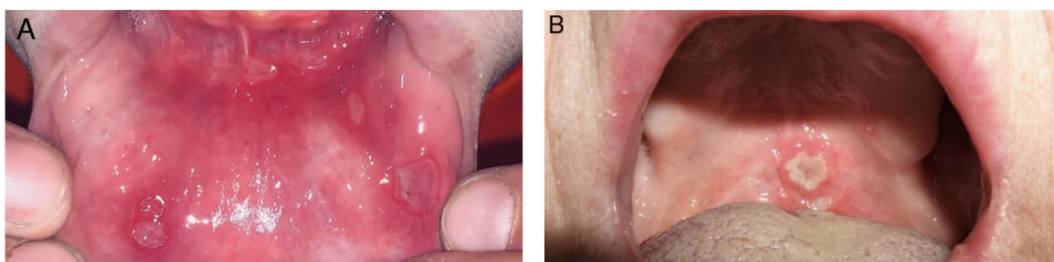


Fig. 7. Depicts both minor and major recurrent aphthous stomatitis (RAS) cases, labeled as A) minor RAS and B) major RAS. Ref. [Sánchez et al., 2020](#).



human leukocyte antigens (HLA) A33, B35, B81, B12, B51, DR7, and DR5 and a lower incidence of HLA-B5 and HLA-DR4 than do healthy individuals (Ślebioda et al., 2014).

### *Symptoms*

Painful, circular, well-defined ulcers with erythematous borders and a grayish-yellow pseudomembranous base are the defining characteristics of recurrent aphthous stomatitis (RAS), which can also affect the lips and tongue (Messadi & Younai, 2010). Up to 48 h before the ulcers form, a burning sensation may be present (Sá et al., 2020). It's possible that the lesions' growth will be accompanied by speech and swallowing difficulties (Barrons, 2001).

Major, minor, and herpetiform are the three clinical manifestations of RAS, and each has a unique morphology, distribution, severity, and prognosis. Despite these variations, all three kinds of RAS greatly affect patients' quality of life and interfere with everyday activities. The regions covered by non-keratinized oral mucosa, particularly the lips, cheeks, floor and vestibule of the mouth, palatal arches, and soft palate, are where the lesions are most frequently found (Rogers, , 1997; Sá et al., 2020; Scully & Porter, 2008). (1) Minor aphthae (Mikulicz aphthae): Manifest as one to five painful ulcers, each less than 1 cm in diameter, typically lasting 10–14 days before they naturally disappear without leaving any scars (Messadi & Younai, 2010). The buccal or labial mucosa, ventral tongue, soft palate, and vestibules are all common sites for these ulcers. Occasionally, depending on the number and severity of lesions, regional lymphadenopathy may be observed. Although the process is self-limited, it may recur with significant unpredictability. Some patients experience almost constant ulcer occurrence, with new ulcers appearing as old ones heal (Messadi & Younai, 2010; Scully, 2006). (2) Major aphthae (Sutton's disease or periaadenitis mucosa necrotica recurrens): These ulcers usually appear during puberty, and chronic recurrences can last for up to 20 years or more (Messadi & Younai, 2010; Scully & Porter, 1989). Ulcers are larger than 1.0 cm in diameter, deeper, and more painful, and can take up to 6 weeks or longer to heal. Both dysphagia and fever are common (Boulinguez et al., 2003; Messadi & Younai, 2010), and scarring is pervasive. Ulcers develop on the labial mucosa, soft palate, or anterior larynx, where they can obstruct eating and jeopardize the patient's nutritional status. Ulcers can be infected with bacteria and/or fungi. (3) Herpetiform aphthous: appear as crops (up to 100) of 1- to 3-mm ulcers that cure in 10–14 days with no scar tissue. They can appear anywhere in the oral cavity

and are frequently misdiagnosed as infections caused by the herpes simplex virus (HSV). Women are more commonly affected, and ulcers typically appear later in life than either major or minor RAU (Messadi & Younai, 2010).

### *Diagnostics and treatment*

On the basis of the history and clinical criteria, RAS is diagnosed. In order to exclude further ulcerative disorders and ailments, a medical history should be obtained. To rule out immunological problems, vitamin and iron shortages, and malabsorption (such as in celiac disease), a complete blood count, hematinic estimation, and anti-endomysial antibody test are recommended (Scully et al., 2003).

There is currently no known cure for RAS. As a result, the primary goals of treatment are to alleviate pain, hasten healing, and reduce the frequency and severity of RAS episodes (Brocklehurst et al., 2012).

When treating aphthae, the proposed plan should consider the patient's medical history, the frequency of breakouts, the severity of the condition, and their tolerance to medication (Baccaglini et al., 2011). Local pharmacological treatments such as antiseptics, anti-inflammatory drugs, analgesics, antibiotics, topical corticosteroids, hyaluronic acid, topical anesthetics, and low-level laser therapy (Irene et al., 2014) have been used to reduce pain, recovery time, and the number and size of ulcers. Low-energy laser therapy using CO<sub>2</sub>, Nd: YAG, diode, and GaAlAs lasers has been found to be particularly effective in treating some cases of aphthae (Akerzoul & Chbicheb, 2018). On the other hand, systemic pharmacological treatments such as antibiotics, corticosteroids, colchicine, dapsone, clofazimine, pentoxifylline, zinc sulfate, immunomodulating agents, and homeopathic substances (Irene et al., 2014) may also be considered depending on the specific condition being treated and other factors (Akerzoul & Chbicheb, 2018; Manfredini et al., 2021). It is important to note that the effectiveness of these treatments varies and should be evaluated on a case-by-case basis.

### **White sponge nevus (WSN)**

#### *History*

White sponge nevus (WSN) is a rare autosomal dominant disorder that generally manifests as white corrugated folds in the bilateral buccal mucosa with a soft texture Fig. 8 (Regezi et al., 2016). Siebenmann was the first to describe this disease as “generalized hyperkeratosis of the skin with involvement of the



Fig. 8. White irregular plaques on the buccal mucosa with well-defined borders and a symmetric distribution. Copyright Dermatological Medicine. Ref: Capatas et al., 2020.

mucosa” in 1908, followed by Hyde in 1909 (Brown & Gorlin, 1960; Cannon, 1935). After that, reports followed on several cases of the same disease, and in 1935, Cannon proposed the name “white sponge nevus of the mucosa” (nevus spongiosus albus mucosae) (Cannon, 1935). There are additional names for WSN, such as Cannon's disease, familial white-folded dysplasia, hereditary leukokeratosis, white gingivostomatitis, and exfoliative leukoedema (Neville et al., 2015; Sanjeeta et al., 2016a). The incidence of WSN is one in every 200,000 people worldwide. Some reports indicated that there is a 3:1 female predominance in being infected with this disease, while the most recent reports showed that both sexes experience the disease at an equal rate (Gupta et al., 2022). The greater part of reported cases occurs either at birth or in childhood, though there have been reports of WSN in adolescents (Regezi et al., 2016).

#### Genetic causes

White sponge nevus (WSN) is attributed to a defect in the normal keratinization process of the oral mucosa, with its underlying cause being linked to mutations in the KRT4 or KRT13 genes. These mutations result in abnormal arrangements of keratin 4 and keratin 13 proteins, which are essential for creating intermediate filaments that provide flexibility and strength to the oral mucosa and other body surfaces. Consequently, the presence of anomalous genetic variants leads to the synthesis of asymmetrical intermediate filaments, rendering the oral mucosa vulnerable to damage from minor trauma or friction during routine activities like eating or teeth brushing. Recent evidence has substantiated the co-expression of both type II KRT4

and its type I counterpart, KRT13, in both the oral and anogenital mucosae, further confirming their role in WSN's pathogenesis. These mutations disrupt intermediate filaments, making the mucosae more susceptible to inflammation, abnormal proliferation, and thickening of epithelial cells, ultimately leading to the clinical manifestation of WSN (Ariani, 2023; Sharma et al., 2018).

#### Symptoms

WSN presents as symptomless pathology: folded lesions that appear as white or gray patches on various mucosal surfaces. These lesions commonly manifest in the buccal, oral base, lingual, and tongue mucosae, as well as the palatal and gingival mucosae; they tend to be thickened and have a spongy consistency, and their size varies depending on the patient himself and the passage of time. The presentation intraorally occurs early in childhood, typically before puberty, and is mostly bilateral and symmetric. Although the disease is painless, patients often mention a variation in the mucosa's texture, which can be observed microscopically. Numerous reports also show episodic burning sensations when eating spicy food in some patients. Skin shows no effect because, in contrast to the mucosa, the skin lacks keratins 4 and 13. It might also develop in the mucosae of the nose, esophagus, rectum, abdominal, and genitalia without the coverage of keratinizing squamous epithelium. The lesions of WSN may bear resemblance to those seen in pachyonychia congenita, hereditary benign intraepithelial dyskeratosis, Darier's disease, and dyskeratosis congenita may resemble (Qiao et al., 2022; Regezi et al., 2016; Sanjeeta et al., 2016b; Songu et al., 2012).

## Diagnostics and treatment

Early diagnosis of the disease is essential to avoid unnecessary treatment and to rule out other, more serious diseases. The diagnosis is confirmed by a biopsy of the lesion and a pathology examination. Since WSN is benign and asymptomatic except for the clinical cases that were mentioned previously, it does not require any treatment (Capatas et al., 2020; Regezi et al., 2016; Sanjeeta et al., 2016b), except for the case of a plaque that extends onto the lip vermilion, in which surgery is used for aesthetic purposes (Marrelli et al., 2012). Treatments with nystatin, antihistamines, vitamins, mouth rinses, azithromycin, tetracycline, and penicillin were used for patients who complained of pain (Songu et al., 2012). Also, treatment with oral doxycycline provided an acceptable aesthetic result. According to some researchers, patients who received topical tetracycline treatment had both partial and full responses. An amount of 0.025% twice a day showed the best results (Amores-Martí et al., 2021). Sometimes a follow-up for a few months is recommended (Aghbali et al., 2009).

## Conclusion

It is crucial to detect, prevent, and treat oral genetic disorders early, as some of them may develop into oral cancer. Advanced diagnostic methods are employed to predict their progression and evaluate the risk of malignancy. This message emphasizes the significance of identifying and preventing oral genetic disorders as soon as possible. The scientific study of oral genetic disorders is still in its early stages, and further research is necessary to improve diagnostic, prognostic, and treatment methods. By enhancing diagnostic and prognostic capabilities, it is anticipated that the clinical management of genetic disorders will be greatly benefited.

## Author contributions

All authors have contributed to the writing and approved the manuscript before submission.

## Conflicts of interest

The authors declare no conflict of interest.

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