Classification, Symptoms, Diagnosis, and Treatment of Oral Genetic Disorders

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ABSTRACT

Infection with some diseases can manifest in the oral cavity through an appearance of ulcers, alterations in color, as well as changes in the size and structure of the oral design. The study focused on examining genetic variants as potential biomarkers for heightened vulnerability to periodontal disease. The objective of this article is to present a comprehensive survey of oral diseases that arise as a consequence of genetic problems. Due to the heightened vulnerability to gum and tooth disease associated with numerous genetic abnormalities, the appearance of these symptoms tends to occur quickly and with notable severity.

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1. Introduction

Several types of hard and soft tissues can be found in the mouth. The tooth possesses a crown and a root. A clinical crown is a section of a tooth that can be observed when it is present in the mouth; it gradually increases with aging and illness, whereas an anatomical crown is a component of the tooth that is covered by the enamel. Additionally, Roots are covered by cementum and do not have visible evidence in the oral cavity of an individual with healthy gums. The expression "periodontium" refers to the alveolar bone, gingiva, cementum, periodontal ligament, and other supporting tissues that surround and protect the teeth. The pulp, a soft tissue, originates in the crown and root's deepest region. The pulp-enamel gap in the crown is widened by the dentin. Dental and periodontal development is a tightly controlled natural process that results from numerous discrete and extremely precise sequences of phases. If any of these developmental phases are impeded or aggravated, the evolved tooth and periodontal structures may differ [1]. A general survey of dental/periodontal abnormalities in humans would be incomplete without some consideration of the etiological factors involving stress, poor diet, smoking, viral and bacterial infection, medical conditions, age, poor hygiene, and genetics [2, 3]. Clinical and basic researchers have been analyzing the relative contributions of hereditary and environmental variables ("nature vs. nurture") in the etiology of dental caries and illnesses of the periodontium for decades. Researchers have investigated gene polymorphisms as potential indicators of a higher vulnerability to periodontal diseases. Heritability researchers show that genetic factors account for 38%-82% of the population variance in the periodontal disease indicators [4]. It becomes clear that genetic factors, including gene-gene interactions and gene-environment interactions (epigenetic factors), may play a significant role in the onset of periodontal disease [3]. Genetic disorders encompass birth defects, chronic illnesses, developmental issues, and sensory deficits inherited from one or both parents. In the current study, we will shed light on the genetic causes and their symptoms, in addition to methods of diagnosis and treatment of some genetic diseases of the teeth and periodontal (Table 1).

Table 1. Some genetic diseases of dental and periodontal disease

Dental	Periodonta
Amelogenesis imperfecta	Hereditary Gingival Fibromatosis
Dentinogenesis imperfecta	Papillon-Lefèvre Syndrome
Tooth Agenesis	
Microdontia	

2. Genetic Diseases of Teeth and Periodontal

In general, genetic syndromes of the teeth and periodontal disease are closely related to neurological, physiological, and anatomical differences in the mouth and its associated structures.

2.1. Dental diseases

2.1.1. Amelogenesis Imperfecta

2.1.1.1. Background

Amelogenesis imperfecta (AI) is inherited in an X-linked manner or as an autosomal dominant or recessive trait. It is considered a heterogeneous disorder that affects the formation, structure, and appearance of enamel in both primary and permanent dentition. As a result of this disorder, enamel has been impacted qualitatively and quantitatively, giving rise to compromised function and esthetics [5]. AI was first reported in 1890 and was not considered a clinical entity distinct from dentinogenesis imperfecta until 1938 [6]. Amelogenesis imperfecta is commonly classified using Witkop's system, which considers phenotype, radiographic traits, and transmission mode. It outlines three core types: hypoplastic, hypocalcified, and hypomaturation. These categories often intertwine, showcasing the intricate spectrum of enamel issues [5]. The prevalence ranged from 1 in 200 to 1 in 8,000, according to the populations studied [7]. Besides that, the presence of AI types: (hypoplastic 60 to 73%, hypocalcification 7%, and hypomaturation 20 to 40%) of all the cases [8] AI was identified as part of a syndrome in cases of amelo-onycho-hypohidrotic syndrome, Kohlschutter syndrome, Morquio syndrome, tricho-dento-osseous syndrome, oculo-dento-osseous dysplasia, epidermolysis bullosa hereditaria, and enamel renal syndrome, among others (Figure 1) [9].

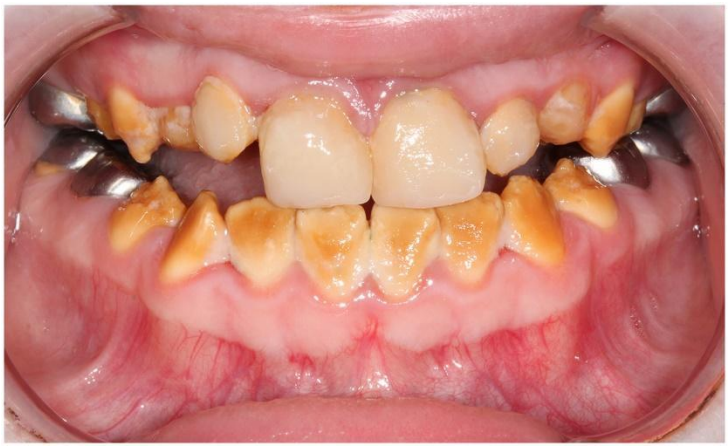

Figure 1: The general appearance of teeth with amelogenesis imperfecta [10]

2.1.1.2. Genetic Causes

Several studies indicate that AI is caused by mutations that occur in 27 genes: AMELX, AMBN, ENAM, LAMA3, FAM83H, AMTN, MMP20, KLK4, WDR72, STIM1, and GPR68 [5, 11]. A number of studies have confirmed ITGB6 as an AI therapeutic target by identifying disease-causing mutations in two AI kindreds [5, 11, 12]. The results of some research indicate that SLC24A4 plays a critical role in the transfer of calcium during enamel formation and that its defect is indicative of impaired enamel formation, while LAMB3 plays a role in early amelogenesis [5, 11]. ODAPH expression was detected in the construction of mouse teeth. The main issue in OdaphC41*/C41* mice begins during the post-secretory transition when ameloblasts fail to mature. ODAPH has been reported to cause recessive hypomineralized amelogenesis imperfecta (AI) in humans [11, 13]. In addition to ACP4, CLDN16, CLDN19, CNNM4, COL17A1, DLX3, FAM20A, LTBP3, SLC10A7, SP6, RELT, and TP63 genes [11].

2.1.1.3. Symptoms

Amelogenesis imperfecta can cause specific oral symptoms such as an enlarged pulp chamber, pulp stones, dens in dente, gingival enlargement, periodontitis, root resorption, short roots, delay in dental eruption, microdontia, deviant crown and morphology, tooth agenesis, crowding of teeth [14], Unusual tooth growth, Uneven, lumpy, or ridged teeth, tooth sensitivity, and Yellow, brown, gray, or white (snow-capping) discoloration of teeth [15]. Other skeletal abnormalities such as open bite, overbite, overjet, and crossbite may also occur [14].

Each type of AI has distinctive symptoms. The symptoms of "hypoplastic AI" include reduced enamel thickness, pitting, and grooves. On radiographs, the hard, translucent enamel in this state contrasts appropriately with the dentin. While in "hypocalcified AI," the enamel looks normal in thickness with weak enamel calcification and an opaque or chalky appearance. Enamel is less radio-opaque than dentine, and teeth rapidly deteriorate and become stained. However, "hypomaturation AI" is associated with enamel of normal thickness that has a mottled appearance, is a little softer than normal, is more prone to dental wear, and has a radiodensity that is equal to dentine on radiographs. Furthermore, "hypoplastic with taurodontism" relates to mixed hypoplasia, hypomaturation, and taurodontism [16].

2.1.1.4. Diagnosis and Treatment

The diagnosis is established based on the clinical presentation alongside an inheritance pattern that may involve X-linked, autosomal dominant, or recessive modes [5]. Treatment depends on the type of AI and the condition's level of severity. Because there is no established treatment for amelogenesis imperfecta. Despite further advancements in methods and expanded accessibility of different dental materials, various studies have shown the utilization of glass ionomer cement. Composites made of resin (direct and indirect restorations), in addition to porcelain veneers, lab-fabricated crowns, stainless steel crowns, partial/complete dentures, and overdentures, can assist with restoring damaged tooth surfaces, and orthodontic treatments may also be considered for patients who have dental or skeletal issues [17]. Admittedly, several AI patients are too young; thus, direct composite restorations are unsuitable, and ceramic crowns are not advised. Research shows an alternate restoration method that falls between direct composite and indirect ceramic methods by employing prefabricated composite veneers and is recommended for the treatment of young AI patients since it offers a functional and aesthetic restoration in one visit with less loss of tooth structure [18]. Children with moderate to severe amelogenesis imperfecta suffer markedly more pronounced oral health-related quality of life as a result of anxiety over-appearance, functionality, and psychological difficulties. When compared to the least affected individuals throughout time, children with AI usually require significant dental care and attend more routine and emergency dental consultations. Increased sensitivity, poor dental hygiene, weakened enamel bonding, and decreased vertical dimension could render treatment challenging [7].

2.1.2. Dentinogenesis Imperfecta

2.1.2.1. Background

Dentinogenesis imperfecta (DGI) is a hereditary autosomal dominant dentin condition that primarily affects the formation of dentin in both primary and permanent teeth (Figure 2) [19]. Other synonyms that describe DGI are hereditary opalescent dentine, opalescent teeth, DGI shields' type II, and capdepont teeth [20]. DGI was first reported by Barret in 1882. while in 1939 Robert and Schour coined the term ‘dentinogenesis imperfecta’ [21]. Three distinct types of dentinogenesis imperfecta with comparable dental defects have been identified by researchers: Type I (DGI-I) develops in patients with osteogenesis imperfecta (OI), a heritable disorder defined by very brittle bones that break or fracture easily (fragile bones), while type II (DGI-II) and type III (DGI-III) usually occur in people without other inherited disorders. The estimated prevalence of DGI-I is 1 in 20,000 births, while DGI-II and DGI-III birth rates are 1 in 8,000 [22].

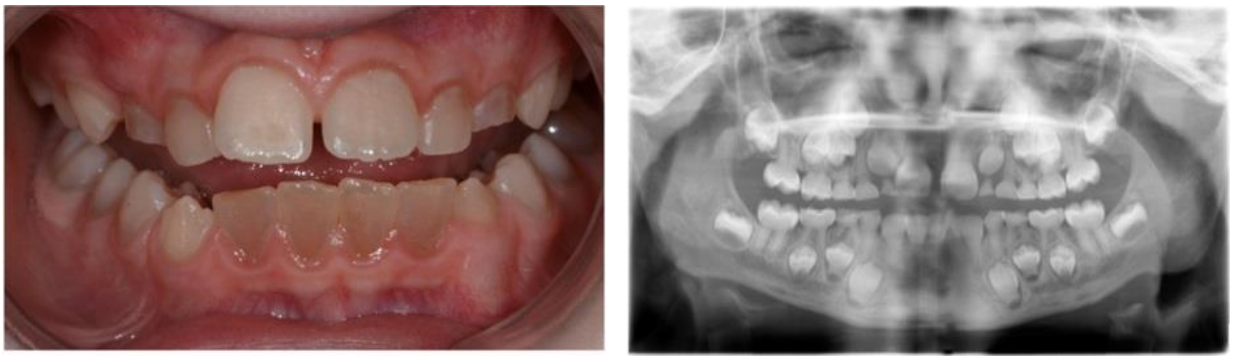

Figure 2: A 10-year-old male with dentinogenesis imperfecta (DGI) during the mixed dentition phase. The permanent dentition shows the most pronounced effects on the mandibular incisors. In the radiographic images from when the boy was 6 years old, distinct features of DGI are evident, including significant narrowing near the base, differing degrees of pulp space reduction, and shortened roots [23].

2.1.2.2. Genetic causes

DGI type I is caused by mutations in the COL1A1 (17q21) and COL1A2 (7q22.1) genes [24], while DGI type II/III are caused by genetic mutations in the dentin sialophosphorylated protein gene (DSPP) on chromosome 4q21. This gene is also associated with other dentin abnormalities known as dentine dysplasia (DD) [25].

2.1.2.3. Symptoms

Severe dentin hypomineralization and abnormal dentin structure are characteristics of dentinogenesis imperfecta [20]. Rapid tooth wear suggests that the primary dentition is more severely affected than the permanent dentition [21, 22]. The teeth are weak and show gray, blue, or amber brown and opalescent discoloration in addition to their diminutive height [22, 26]. Altered enamel dentin junction causes enamel loss and dislodgement. Dentin attrition might cause the crown to completely vanish or even cause minor erosion [23]. The crowns of the teeth have a pronounced cervical constriction that gives them a "bulbous" appearance, while the roots are short and thick, and the canals and pulp chambers have been obliterated [20].

2.1.2.4. Diagnosis and Treatment

Early detection and management of DGI are advised, as they may slow or stop the deterioration of the teeth and occlusion and enhance aesthetics. To stop tooth wear and maintain the occlusal vertical dimension, stainless steel crowns can be placed on the deciduous molars. Using composite strip crowns or composite facings can further elevate the aesthetics [20]. Over-dentures are a treatment option for individuals who have significantly eroded or abraded teeth to the gingival level [26]. Overdentures are regularly endured by children, yet as they grow, they should be checked often and refabricated. Pulp therapy is not beneficial if abscesses develop; the affected teeth must be extracted. General anesthesia might be required to facilitate treatment in children who need an extensive number of procedures and of weak cooperation. When the permanent dentition starts erupting, the tooth wear rate must be frequently monitored. Cast occlusal onlays may be advantageous for the first permanent molars and later the premolars to lessen tooth wear and preserve the occlusal vertical dimension until the child reaches adulthood, but the emphasis ought to be on conservative tooth preparation. Full mouth rehabilitation may be considered if it is clinically essential at this point in time [20]. In cases where only a few teeth are missing, either conventional dentures that can be taken out or prosthetics anchored by dental implants can be used to restore oral function and appearance [26].

2.1.3. Tooth Agenesis

2.1.3.1. Background

Tooth agenesis (TA) is the medical term for missing teeth, which is one of the most common congenital disorders that affect both dentitions (Figure 3). It is inherited either in a Sex-linked manner or in an autosomal dominant or recessive pattern [27]. Mandibular second premolars were reported to be the most frequently missing teeth in most studies, followed by maxillary lateral incisors [28]. The estimated prevalence of losing at least one third molar is up to 25% of the total population. The absence of other permanent teeth -excluding third molars- ranges from 1.6 to 9.6%, depending on the individuals under study. Deciduous teeth may likewise be affected, albeit to a lesser extent (from 0.5 to 0.9) [29]. Tooth agenesis may appear as a complete absence of teeth, which is referred to as Anodontia. Some people are born missing some, but not all, of their teeth. Hypodontia is another type of dental agenesis, specifically referring to one to six missing teeth, while oligodontia is when six or more teeth are missing. Both hypodontia and oligodontia are termed as partial anodontia [30]. The Online Mendelian Inheritance in Man (OMIM) database covers approximately 60 syndromic disorders that highlight hypodontia as a feature of their phenotypic range of abnormalities. Disorders that are associated with hypodontia include Witkop syndrome, oral-facial-digital syndromes, as well as syndromes characterized by oral-facial clefting such as Van Der Woude syndrome and Pierre-Robin sequence [31].

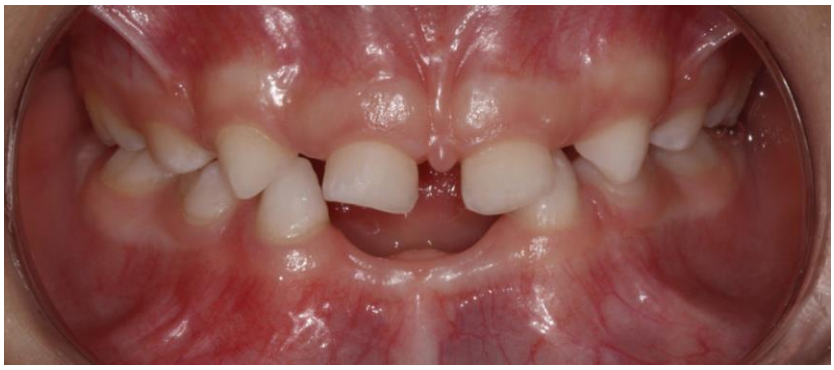

Figure 3: The general appearance of teeth with Tooth Agenesis [32]

2.1.3.2. Genetic causes

As mentioned earlier, TA is a congenital, inherited disorder caused by mutations in certain genes. The most reported genes were AXIN2, EDA, MSX1, and PAX9. Other genes identified as strong causative agents include: LRP6, WNT10A, WNT10B, EDAR, SMOC2, DKK1, GREM2, LTBP3,

EDARADD, KREMEN1, and BMP4. Pathogenic or likely pathogenic nucleotide changes were observed in 56.92% of those affected, including eight nucleotide alterations of genes not previously implicated in non-syndromic tooth agenesis (CHD7, CREBBP, EVC, LEF1, ROR2, TBX22, and TP63) [33].

2.1.3.3. Symptoms

It is usually detected clinically by x-ray when there is no tooth eruption or tooth bud visible on the radiograph. Other symptoms may appear in people that are associated with TA, such as taurodontism [34] and the reduction of dental crown size dimension, which may appear as pig-shaped teeth [29]. Tooth agenesis is usually associated with chewing and speaking difficulties, Ectodermal dysplasia, Down syndrome, and other systemic illnesses. There are various reasons for a putative link between congenital tooth absence and facial skeletal pattern [35]. In some cases of tooth agenesis, mutations in some genes lead to abnormal alveolar bone. The alveolar bone is not properly developed, which makes dental implant surgery more difficult because the implant is acting as an artificial root and must be placed into a healthy alveolar bone [36].

2.1.3.4. Diagnosis and Treatment

Tooth agenesis cases require planning a comprehensive treatment over a long period of time for optimal lifelong results. Therapeutic management of patients with partial anodontia demands a team with diverse disciplines, including the pedodontist, orthodontist, prosthodontist, and maxillofacial surgeon. The extent of crowding, malocclusion type, periodontal conditions, the patient's age, alveolar process bone volume, facial profile, vertical or horizontal growth pattern, craniofacial morphology, and the number of missing teeth should be incorporated into the treatment plan [37]. For patients with partial anodontia, two treatment options are considered: space reopening and space closure. The possibility of reopening space for implant insertion, autotransplantation, and prosthetic restoration exists. Fixed orthodontics can be used to close the spacing. The most successful treatments for full anodontia are complete (fixed and removable) dentures or dental implants [38].

2.1.4. Microdontia

2.1.4.1. Background

Microdontia is a condition in which the size of one or more teeth is physically reduced [39]. This disorder is inherited in an autosomal dominant pattern, but an autosomal recessive mode of

inheritance has also been reported [40]. Tooth size varies by race and gender (Males have larger teeth than females). Some describe abnormal tooth size as when the dimensions differ by more than two standard deviations from the norm. Specialists regard such teeth as microdontic teeth, or simply microdonts [39]. Boyle states that " in general microdontia, the teeth are small, the crowns are short, and normal contact areas between the teeth are frequently missing.". Shafer, Hine, and Levy divide microdontia into three distinct groups: (1) single tooth microdontia; (2) relative generalized microdontia owing to small teeth size in big jaws; and (3) true generalized microdontia, a condition in which all of the teeth are smaller than average [41]. The proportion of abnormalities varies by tooth region and can be attributed to development time. Teeth that develop later within the same location are more variable than teeth that develop initially [42]. Microdontia affects between 0.2% and 0.5% of deciduous teeth and 0.5% to 3.1% of permanent teeth, predominantly the maxillary lateral incisor teeth, known as peg laterals (1.8%). Females are more likely to be afflicted than males [43].

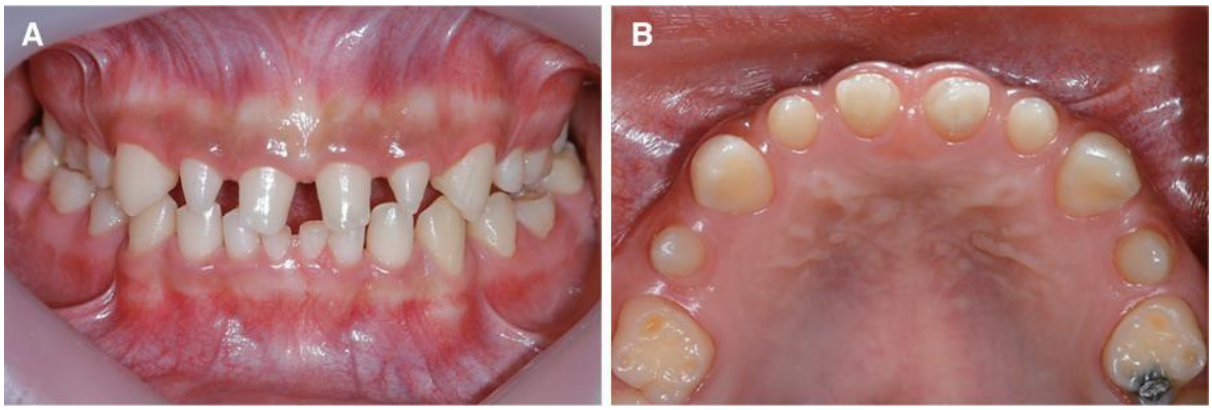

Figure 4: The general appearance of teeth with Microdontia (A) Frontal view, (B) Occlusal view of the maxillary arch [44].

2.1.4.2. Genetic causes

More than 350 genes related to dental development have been identified, including PAX9, AXIN2, EDA, EDAR, and WNT10A. Additionally, mutations of the MSX1 gene, which is found to be the most common cause of microdontia. However, few genetic studies have shed light on how genes are linked to this condition [45]. According to some reporters, rs8018720 in SEC23A was associated with a third molar microdontia in the co-dominant [40].

A study of thirteen single nucleotide polymorphisms in the PAX9 gene on chromosome 14q13.3 reported that both rs12881240 and rs2295222 SNPs were polymorphic and had a clear relationship with peg-shaped teeth. Polymorphisms in the PAX9 gene cause a partial failure of incisor and third molar tooth formation as well as a disruption in dentin genesis differentiation [46]. However, studies are still ongoing on the relationship of genes to microdontia [45].

2.1.4.3. Symptoms

Microdontia can be identified by small or cone-shaped teeth. The small size may be attributed to the reduced size of the teeth themselves in conditions of true generalized microdontia and localized microdontia, or their appearance may appear small despite their normal size due to the larger jaw in relative microdontia, and this may occur as a result of inheriting one parent's oversized jaw and standard-measured teeth from the other parent [47, 48]. This phenomenon can manifest in either isolated, which is fairly common [49] or associated with other syndromes such as Gorlin-Chaudhry-Moss syndrome, Williams's syndrome, Chromosome d/u, 45X [Ullrich-Turner syndrome], Chromosome 13 [trisomy 13], Rothmund-Thomson syndrome, Hallermann-Streiff, Oculo-mandibulo-facial syndrome, Tricho-Rhino-Phalangeal, type1 Branchio-oculo-facial syndrome [41], and also with Down’s syndrome, pituitary dwarfism [39].

2.1.4.4. Diagnosis and Treatment

It is crucial to gather information concerning the patient's medical, family, and dental history [43], especially in the case of tooth agenesis. This is the relevant aspect of history taking in patients with microdontia. The clinical diagnosis of microdontia is typically established upon its eruption or radiographically if it does not erupt [47]. To inhibit cyst development, the unerupted microdontia should be surgically removed, whereas in the case of erupted microdontia, there are several options for treatment courses depending on the severity, the patient's preferences, functional needs, and aesthetic requirements determine the course of treatment. Extraction is followed by the placement of an implant or a fixed prosthesis, orthodontic treatment to correct its position, and restorative treatment to restore teeth. The less conservative options are indirect restorations such as crowns and porcelain veneers. To prevent injury to soft tissues, very conical and sharp canine teeth may need to be reshaped [43]. The Medical Research Institute at Kitano Hospital in Japan conducted a groundbreaking trial focused on individuals with anodontia. By identifying a connection between the USAG-1 gene and tooth growth constraints in mice, the team progressed to experiments targeting the suppression of USAG-1 expression. Notably, their successful employment of anti-

USAG-1 antibody treatment in mice demonstrated its potential for tooth regeneration, offering a promising avenue for addressing tooth abnormalities in humans. This study highlights the potential of oligonucleotide therapies, such as siRNA, in promoting tooth regeneration and the use of cationized gelatin as an effective drug-delivery system for siRNA-loaded mandibles. These findings offer hope for individuals with congenital tooth agenesis and other tooth abnormalities, paving the way for future research in the field of regenerative dentistry [50].

2.2. Periodontal diseases

2.2.1. Hereditary gingival fibromatosis (HGF)

2.2.1.1. Background

Hereditary gingival fibromatosis (HGF), also known as gingivomatosis, gingival hyperplasia, elephantiasis gingivae, familial elephantiasis, the gigantism of the gingiva, congenital macrogingivae, gingival enlargement, or gingival overgrowth (GO) [51], is a rare genetic disease that can manifest as an isolated disease, part of a syndrome, or as a result of chromosomal abnormalities. It is characterized by a slow progression of gingiva enlargement (Figure 5) [52]. Goddard and Gross were the first to report HGF in 1856 [53]. Studies concluded that both males and females are equally affected. The prevalence according to phenotype is 1:175,000, while according to genotype it is 1:350,000 [54]. Although autosomal-dominant traits are reported more commonly, There have also been reports of autosomal-recessive inheritance [52]. This abnormality has been divided into two types based on its appearance: the localized nodular type, which is distinguished by many gingival enlargements, and the gingiva that enlarges uniformly in the symmetric form of the disorder, which is the most prevalent form [55]. Many syndromes are related to HGF, including Amelogenesis imperfecta, Juvenile hyaline fibromatosis, Zimmermann-Laband syndrome, Jones syndrome, Prune-belly syndrome, Klippel-Trenaunay-Weber syndrome, and Ramon syndrome [54].

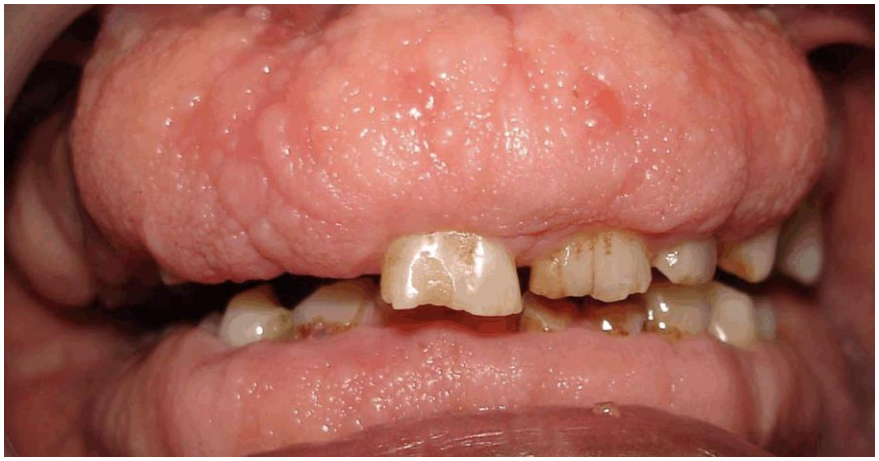

Figure 5: The general appearance of teeth with Hereditary gingival fibromatosis (HGF) [56]

2.2.1.2. Genetic Causes

Several studies reported mutations in chromosomes 2, 5, 11, and 4, more specifically 2p21-p22, 2p22.3-p23.3, 5q13-q22, 11p15, and 4q12 are related to HGF [57, 58]. Gene loci like GINGF2, GINGF3, and GINGF4 are defined as candidate loci of HGF [52, 57, 58]. Two genes, REST and SOS1, have been identified as having a clear relationship to the HGF disease [52].

2.2.1.3. Symptoms

The most typical form of HGF has a rose color, a fibrous appearance, and noticeable stippling with no sign of inflammation [59]. HGF manifests as a benign, slowly progressing, and non-hemorrhagic enlargement of the gingiva. The increased collagen formation in the gingival corium is the cause of this gingival overgrowth [60]. The masticatory mucosa is affected, although it does not progress past the mucogingival junction. Clinically, the condition rarely manifests at birth and typically begins with the emergence of deciduous or permanent dentition. HGF can also manifest locally as a nodular-like lesion. In addition to diastemas, teeth displacement, or the retention of primary or impacted teeth, excess gingival tissue can cover a portion of the crown or the entire tooth, and it can also lead to phonetic, psychological, esthetic, and masticatory issues [61]. Several clinical manifestations, including hypertrichosis, epilepsy, mental retardation, hearing loss, hypertelorism, supernumerary teeth, and growth hormone deficiency, have also been linked to HGF [62, 63].

2.2.1.4. Diagnosis and Treatment

HGF is commonly diagnosed based on a clinical and periodontal examination, a medical and family history, and laboratory tests [64]. Treatment requirements vary depending on the severity. When the enlargement is at its finest, good dental scaling and home care are required to maintain good oral health. Increased gingival mass, for functional and aesthetic settlement, the case will necessitate surgical intervention. Gingivectomy is the most common method [56]. The CO2 laser is also used as a surgical technique considering its ability to coagulate and seal blood vessels, vaporize the tissue, make an accurate incision, and improve the healing effect due to its antimicrobial properties [65]. A periodontal flap procedure might be preferred if osseous defects and attachment loss are present along with fibromatosis [62]. For optimal results, it is advisable to initiate therapy once the permanent teeth have fully emerged. Recurrence of the condition often happens within varying time frames. Several authors suggest that the likelihood of recurrence can be significantly reduced by postponing the gingivectomy until the permanent dentition is established [63].

2.2.2. Papillon-Lefèvre Syndrome

2.2.2.1. Background

In 1924, Paul Philippe Henri Lefèvre and Paul Henri Papillon published the first description of the Papillon-Lefevre syndrome (PLS). This disease is an autosomal recessive condition and exceedingly rare, with a prevalence of 1- 4 cases per million and no sexual or racial predominance. It's classified as ectodermal dysplasia, and it is inherited as an autosomal recessive condition (Figure 6). It is characterized by severe generalized early-onset periodontitis and palmoplantar hyperkeratosis, which result in the early loss of both dentitions. Without genetic testing, PLS might easily be confused with psoriasis. It is also known as “keratoris palmoplantaris with periodontopathia” and “hyperkeratosis palmoplantaris with periodontosis” [66, 67].

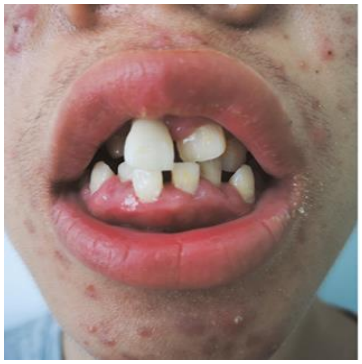

Figure 6: The general appearance of teeth with Papillon-Lefèvre Syndrome [68]

2.2.2.2. Genetic Causes

A mutation in the cathepsin C gene (CTSC) is the only known cause of this condition, and it can be found on human chromosome 11q14.2. The CTSC gene plays a crucial role in activating proinflammatory proteases, regulating immune cell function, and controlling the formation of the corneocyte envelope. Pathogenic variants responsible for Papillon-Lefèvre syndrome (PLS) are primarily found in exons 5-7, which encode the heavy chain of cathepsin C. This indicates that the formation of tetramers is essential for the enzyme's activity. It is important to note that most PLS patients exhibit compound heterozygosity, except those from consanguineous families. Interestingly, even when the CTSC gene mutations are identical, they can result in different phenotypes. So far, there are no established direct correlations between genotypes and phenotypes. The mechanism underlying the diverse phenotypes resulting from identical CTSC gene mutations remains incompletely understood and may involve other genetic and environmental factors [69].

2.2.2.3. Symptoms

When it comes to oral involvement, the first clinical signs develop soon following the emergence of deciduous dental elements. By the age of 2-3 years, periodontal Symptoms become visible. Plaque accumulation, severe gingivitis, periodontitis, and numerous cavities are examples of primary oral manifestations affecting teeth. Following the full emergence of the primary dentition, erythematous oral mucosa with perioral lymphadenopathies and halitosis might be observed. In some cases, it may have microdontia and incomplete root formation. Periodontal abscesses are frequently seen on teeth, and gingival tissues next to the dental elements are often inflamed, edematous, and painful to the touch, whereas those in edentulous regions appear healthy. After losing all of the primary dentition, gingival inflammation disappears, and the oral mucosa appears healthy [70]. Permanent dentition symptoms are comparable to those of deciduous teeth [71]. PLS

might also affect the palms and soles, and palmoplantar hyperkeratosis can spread to the dorsal surfaces of the hands and feet [68]. Fortunately, despite the absence of NSPs in immune defense cells, there is no apparent immunodeficiency [66].

2.2.2.4. Diagnosis and Treatment

The diagnosis of PLS is difficult despite the wide range of symptoms and indications. Clinical symptoms are used to make the diagnosis, and genetic testing is used to confirm it. Apart from palmoplantar hyperkeratosis, Papillon-Lefèvre syndrome stands out among monogenic disorders that are accompanied by periodontitis because periodontal inflammation predominates in the clinical diagnosis [72]. Several treatment options have been proposed, including periodontal treatment in the form of scaling and root planing as well as pharmacological therapy (antibiotic treatment) to manage active periodontitis and avoid bacteremia and eventual pyogenic liver abscess, a complication of PLS due to immune system impairment [73]. To replace the missing teeth after the loss of deciduous teeth, prosthetic therapy will be required. The prosthetic treatment will be made using partial or full dentures, and it will be age-specific. implant-supported over-dentures are generally recommended for edentulous patients with PLS. Early removal of periodontally-involved permanent teeth has been advocated as a form of treatment to protect alveolar bone [74]. Currently, there are no other treatment options besides periodontal treatment and prosthetic therapy for PLS. However, researchers are looking into possible gene therapies and other treatments that could assist to address the condition's underlying genetic origin.

3. Conclusion

In summary, the findings reported in the main body of the research suggest that oral disease can possibly develop due to hereditary factors, which may be influenced by the interaction between genetic features and environmental conditions. The cause of dental diseases includes a wide range of hereditary factors. The expression and degree of manifestation can be influenced by a variety of factors, including the specific gene involved and the kind and site of the genetic alteration. The etiology of dental illness remains incompletely understood by researchers, with genetic factors being recognized as one of the significant contributors that cannot be disregarded. Potential advancements in healthcare, particularly in the realm of genetic manipulation pertaining to tooth production, have the potential to pave the way for gene treatments and the growing of dental tissues through the utilization of dental stem cells.

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الاضطرابات الوراثية الفموية: التصنيف، الأعراض، التشخيص وطرق العلاج

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المستخلص

غالبًا ما تظهر القروح والتغيرات في اللون ، بالإضافة إلى حجم وبنية تجويف الفم ، نتيجة الإصابة ببعض الأمراض. لذلك أجرى العديد من الباحثين العديد من الأبحاث لفهم أسباب هذه الأمراض ، ووجدوا أن الاضطرابات الوراثية هي أحد اهم المؤشرات المحتملة لزيادة القابلية للإصابة بأمراض اللثة. تهدف الدراسة الحالية إلى تقديم لمحة عامة عن بعض أمراض الفم الناتجة عن الاضطرابات الوراثية. نظرًا لأن العديد من الاضطرابات الوراثية تزيد من قابلية المريض للإصابة بأمراض اللثة والأسنان ، فإن الأعراض الأخيرة تظهر بسرعة وشدة نسبيًا.