10.5005/jp-journals-10024-1596

REVIEW ARTICLE

Single Gene Disorders with Craniofacial and Oral Manifestations

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ABSTRACT

Gene and environmental factors are instrumental in genesis of complex and wide range of disorders and syndromes. The newer gene sequencing and other advanced technologies have made our previous knowledge of genetic etiopathogenesis of various disorders more transparent. Single gene disorders refer to the disorders caused due to mutations in a single gene and a fair number of these manifest as craniofacial defects and anomalies. This review is an attempt to give a detailed insight into the varied single gene disorders and syndromes with an emphasis on dental implications.

Keywords: Single gene syndromes, Autosomal, X-linked, Dominant, Recessive, Inheritance, Gene mutations, Craniofacial syndromes, Oral manifestations.

How to cite this article: Patil S, Rao RS, Majumdar B. Single Gene Disorders with Craniofacial and Oral Manifestations. J Contemp Dent Pract 2014;15(5):659-671.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

In the past decade, there has been enormous advancement in the field of genetic research, which has added new dimensions to the knowledge of various genetic disorders and related diagnostic and therapeutic modalities. With the completion of Human Genome Project, it is now known that two individuals share 99.5% of their DNA sequences and less than 0.5% of the DNA encodes for the human diversity.[1] Thus, the mystery of various health-related disorders must be inherent as compared to this small percentage of variations. With the advent of newer gene-sequencing technologies, remarkable success has been achieved in identifying the causes of single gene and other rare genetic diseases.

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The genetic disorders can be broadly categorized into[1]:

1. Single gene disorders.
2. Chromosomal disorders.
3. Complex multigenic/polygenic disorders.

The frequency of genetic diseases is estimated to be 670 per 1000.[1] About 2 to 3% of newborns present with congenital anomaly and more than half of that represent the head and neck region.[2] Hence, it is of utmost importance for the dental surgeons to understand the basis of development of these anomalies.

SINGLE GENE DISORDERS

Mutations in a single gene can manifest as complex syndromes including craniofacial and other organ anomalies. Single gene disorders are also known as Mendelian disorders, as the phenotype inheritance pattern follows the Mendel's laws of inheritance.[1] According to studies, it is estimated that 85% of these mutations reside in approximately 1 to 1.5% of genome, which consists of exons.[1]

Modes of inheritance of single gene disorders can be autosomal (i.e. involving chromosomes 1-22) or sex-linked (i.e. involving X or Y chromosomes), which can either have a dominant or recessive trait. But the phenotypic features of an individual depend on the penetrance and expressivity of these traits. Penetrance refers to how often a trait is expressed in an individual, whereas expressivity refers to how much that trait affects the individual. Sometimes both of the alleles of gene pair contribute to the phenotype leading to a condition called co-dominance. In addition, a single gene mutation may result in multiple manifestations (pleiotropism) or conversely, mutations at several genetic loci may produce a singular trait (genetic heterogeneity).[1] Various inheritance patterns are as follows:

1. Autosomal inheritance pattern:
   a. *Dominant trait*: It manifests in a heterozygous state. A single copy of the mutant allele is enough to manifest the disease. These traits can be traced through many generations in a family and has a vertical mode of transmission. Both males and females are affected equally and affected person carries 50% chance of transmitting the mutant gene (Fig. 1). Although the genotypic inheritance is dominant, the phenotypic features of the trait depends on the penetrance and expressivity, and in some cases environmental factors.

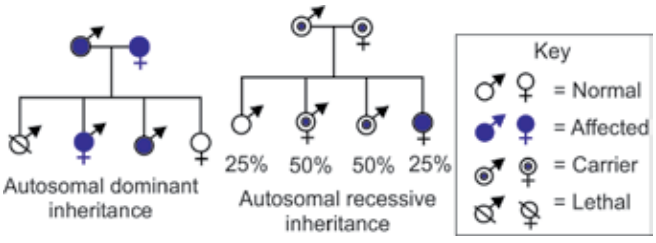

Fig. 1: Autosomal inheritance pattern

Fig. 2: X-linked dominant inheritance pattern

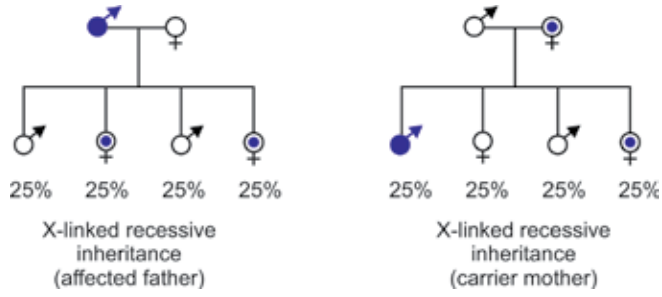

Fig. 3: X-linked recessive inheritance pattern

b. *Recessive trait*: It manifests in a homozygous state, i.e. two copies of the mutant allele is required to manifest the disease. If an individual receives only single copy of the mutant allele, the person is said to be a carrier and does not manifests the disease. These traits are seen in single sibship or consanguinity cases and follow a horizontal mode of transmission. If both the parents are carriers, then there is a 25% chance of having an affected child (Fig. 1).

2. X-linked inheritance pattern:
   a. *Dominant trait*: The mutant allele is located in the X chromosome and a single copy of mutant allele can manifest the disease. It resembles autosomal dominant pattern of inheritance. Both sexes are affected. In case of affected female, 50% of transmission is seen in both the male and female progeny, whereas an affected male transmits the mutant allele to all his daughters and none to his sons (Fig. 2).
   b. *Recessive trait*: The trait present on the X chromosome manifests only in males, as they are hemizygous for that allele. The affected male transmits the mutant allele to all his daughters who become obligate carriers. The disease is transmitted by the obligate female carriers to 50% male progeny (affected) and 50% female progeny (carriers) (Fig. 3). Diagonal mode of transmission is seen.

In both traits, there is no male-to-male transmission observed.

3. Y-linked inheritance pattern: The mutant allele is present only on the Y chromosome. Only males and their male progeny are affected. Diseases caused by this mutation are most unlikely apart from male infertility.[1,3]

GENES AND MUTATIONS

Normal Gene

The term gene was coined by Willard Johannsen in 1920s, which superseded the earlier terminologies like inheritance factor or inheritance unit. The genes are the functional unit of the DNA that can be transcribed, whereas an allele is considered as an alternative form of a gene.[1,4] The structure of mammalian genes include exons and introns, which are the coding and noncoding regions respectively. There is extensive variation in the number of introns, ranging from only two in the case of the globin genes to about 50 in the gene coding for the α-chain of collagen. The function of exons is to code for the functional proteins, whereas the introns separate the coding regions from one another though their function is poorly understood (Fig. 4). It has been suggested that they may offer an evolutionary advantage by increasing the speed at which selection for functionally useful DNA fusion products might be produced by various recombination events.[5] The main functions of genes are that they serve as a template for synthesis of various proteins and functional RNAs, and aids in the transmission of various traits from parents to progeny.[4]

Mutations

Mutation is defined as a permanent change in the structure of DNA. Identification and location of the mutated or abnormal genes first require to identify the families where these defects can be traced for many generations. Next, the chromosome locus for the defect is located with the help of DNA linkage analysis. Next step would be location of the defective gene within the chromosome locus with the help of polymerase chain reaction (PCR) and other latest techniques available.

Mutations in germ cells manifest as hereditary diseases, whereas mutations in somatic cells are responsible for cancer and some congenital malformations. Mutations are of mainly two types:

1. *Point mutations*: It refers to the replacement of one base pair by the other. It is of two types.
   a. *Transitions*: A purine-pyrimidine base pair is replaced by another base pair.

Fig. 4: Coding and noncoding regions present on a DNA strand

b. *Transversions*: Purine is replaced by a pyrimidine base and vice versa.

Consequences of point mutations include (Fig. 5):

a. *Silent mutation*: There are no detectable effects in this type of mutation, as the changed base may code for the same amino acid.
b. *Missense mutation*: In this, the changed base may code for a completely different amino acid, e.g. Apert's syndrome.
c. *Nonsense mutation*: It forms the termination codon, which in turn stops synthesis of amino acid, e.g. cystic fibrosis.

2. *Frameshift mutation*: These mutations occur when one or more base pairs are inserted or deleted from the DNA causing insertion mutation and deletion mutations. Hence these mutations are also called indel type of mutations (Fig. 6).

Frameshift mutations lead to an altered reading frame of mRNA which may further lead to protein synthesis with several altered amino acid or prematurely terminated proteins, e.g. Lesch-Nyhan syndrome (HGPRT), osteogenesis imperfecta.[4-6]

EXAMPLES OF SINGLE GENE DISORDERS WITH ORAL MANIFESTATIONS (FLOW CHART 1)

Apert's Syndrome

Wheaton in 1894 first described the syndrome followed by a comprehensive review by Apere in 1906. It is characterized by premature fusion of the skull bones and shares approximately 5% of all craniosynostosis syndromes with a prevalence of 1 in 65,000 to 160,000 live births. Inheritance pattern is autosomal dominant with the defective gene FGFR2 located in the 10q25 to 10q26 chromosomal locus.[7,8] It is an example of missense mutation.

General and Craniofacial Features

The disorder is characterized by severe craniosynostosis, symmetric syndactyly of the hands and feet, brachycephaly, flat occiput, proptosis, low set ears, midface hypoplasia, hypertelorism and a short, broad nose with a bulbous tip.

Oral Manifestations

Prominent oral features include:

Hard tissue defects include arched palate with bilateral swellings of the palatine processes, resulting in a pseudocleft in the midline, delayed or ectopic eruption and malocclusion, impaction, severe crowding, shovel-shaped incisors, sometimes supernumerary teeth or multiple congenital missing teeth, class III malocclusion, anterior open bite, bilateral and unilateral (lesser extent) posterior crossbite and midline deviation.

Soft tissue defects include hypotonic lips, bifid uvula and thickened gingiva.[9]

Beare-Stevenson Cutis Gyrata Syndrome

The syndrome is a rare autosomal dominant condition with characteristic skin manifestations, distinguishing it from other similar syndromes involving craniosynostosis with meager 20 reported cases reported in literature. It occurs due to point mutations involving FGFR2 gene located in 10q26.13 chromosomal locus. Recently two different mutations, p.Y375 and p.S372C, both in exon 10 of the gene were identified.[8,10]

General and Craniofacial Features

Prominent features include craniosynostosis, cloverleaf or turricephalic skull shape, choanal atresia, midface hypoplasia, cutis gyrata (skin furrows with a corrugated appearance of the scalp, face, neck, palms and soles), ocular hypertelorism and proptosis, acanthosis nigricans, cutaneous skin tags, ear defects, anogenital anomalies and a prominent umbilical stump.

Oral Manifestations

Associated dental features include presence of natal teeth, hypodontia, palatal abnormalities like clefting, a bifid uvula and a narrow or high-arched palate.[11]

Crouzon Syndrome

Crouzon syndrome is inherited as an autosomal dominant disorder with complete penetrance and variable phenotypic expression with prevalence of approximately 1 in 25,000.[12] The various defects arise due to mutation in the FGFR2 gene located in 10q25 to 10q26 chromosomal locus.

General and Craniofacial Features

The features includes craniosynostosis, acoustic meatus atresia and malformations of the middle ear leading to conductive hearing loss. The obstruction of the upper respiratory passages lead to acute respiratory anxiety, dyspnea, mainly when connected to upper maxillary hypoplasia. Ocular abnormalities are shallow orbits, bilateral ocular proptosis, hypertelorism, divergence strabismus, optical atrophy, conjunctivitis or exposure keratoconjunctivitis and loss of visual accuracy. Prominent facial features include a high and large forehead, with convexity in the region of the anterior fontanel, flattening of the occipital region and maxillary

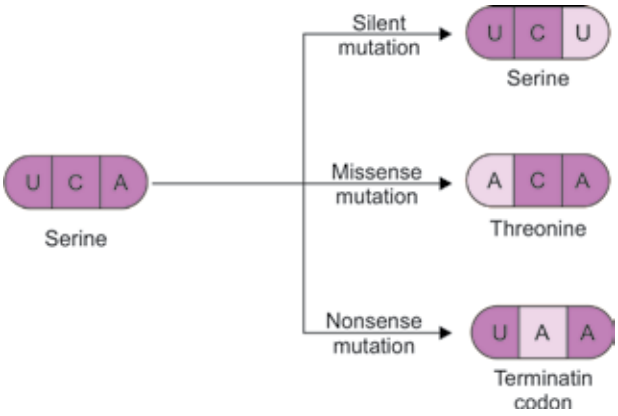

Fig. 5: Consequences of point mutations

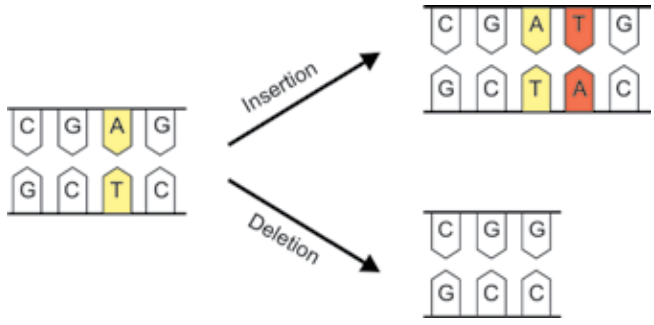

Fig. 6: Types of frameshift mutations

hypoplasia, which are responsible for appearance of the patient. The nose shows a 'parrot beak' appearance due to the frontal shortening of the dorsum of nose.

Oral Manifestations

Mandibular prognathism, overcrowding of upper teeth and V-shaped maxillary dental arch. Narrow, high or cleft palate and bifid uvula may also be seen. Occasional oligodontia, macrodontia, peg-shaped, and widely spaced teeth have been reported.[12] Other features include class III occlusion and maxillary dental arch in 'V' shape with spaced teeth.[13]

Cleidocranial Dysplasia

Cleidocranial dysplasia was first reported by Meckel in 1760 and the term was proposed by Marie and Sainton. It is an uncommon bone disorder with autosomal dominant inheritance pattern with a prevalence of 1 in 1,000,000 approximately. The manifestations are caused by defect in gene RUNX2, located in 6p21 chromosomal locus, which encodes for CBF1 transcription factor, which dictates the osteoblastic differentiation and bone formation.

General and Craniofacial Features

Include short stature, hypoplasia/aplasia of the clavicles, resulting in hypermobility of the shoulders, dysplastic muscle attachments to the clavicles, causing distortion of the

Flow Chart 1: Working classification of single gene disorders with oral manifestations

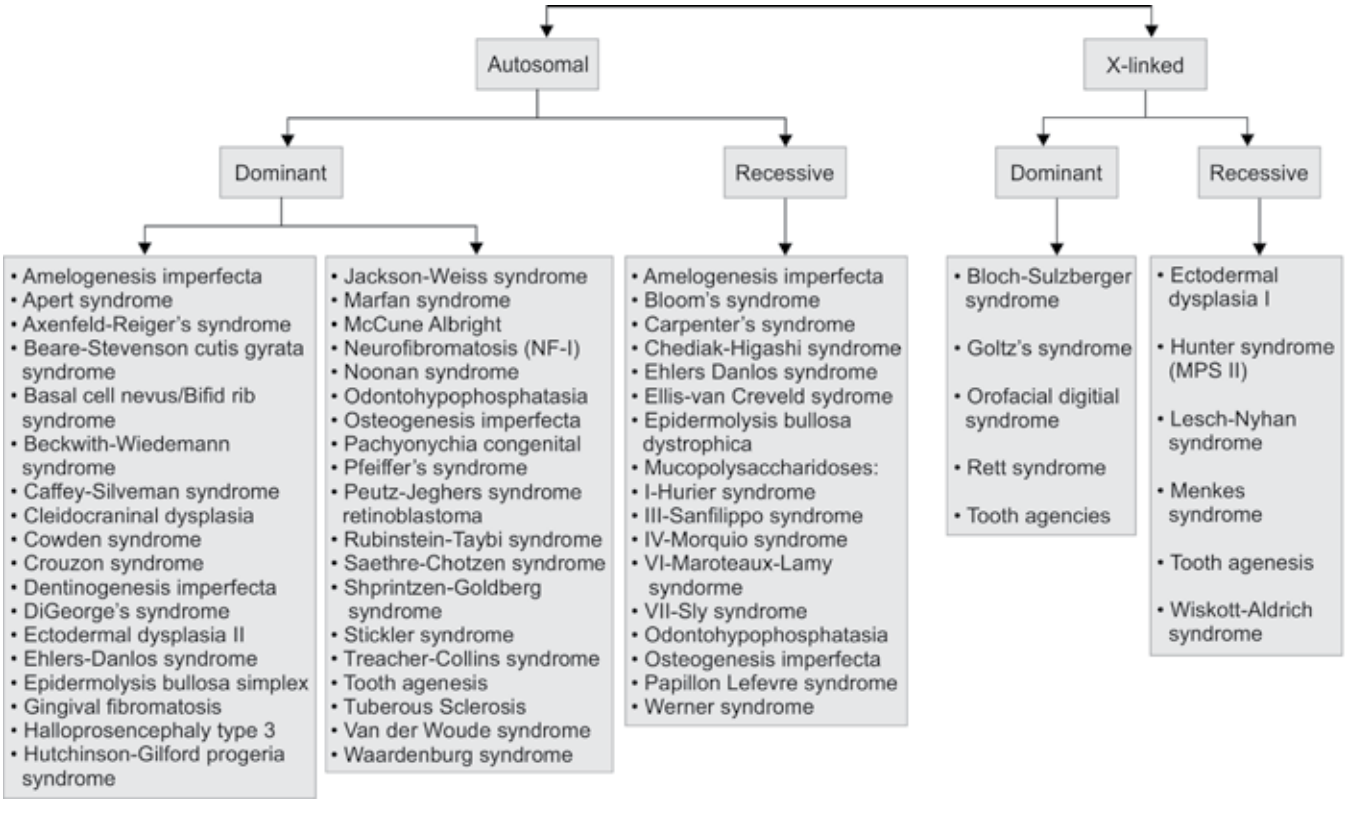

Table 1: Single gene disorders with minor oral involvement

Syndrome		*Gene*	*Chromosomal locus*	*Inheritance*	*Oral manifestations*
Jackson-Weiss syndrome		FGFR2	10q25 to 10q26	AD	Midface hypoplasia[35]
Saethre-Chotzen syndrome		TWIST	7p21.1	AD	Cleft palate, maxillary hypoplasia[36]
Shprintzen-Goldberg syndrome		SKI	1p36.33	AD	Micrognathia, narrow high arch palate[37]
Pfeiffer's syndrome		FGFR1	8p11.23 to 8p11.22	AD	Midface hypoplasia[38]
		FGFR2	10q26.13		
Amelogenesis imperfecta		AMLEX	Xp22.31 to Xp22.1	AD and AR	Hypoplastic enamel[39]
			4q13.3		
		ENAM	11q22.3		
		MMP20			
Basal cell nevus/ Bifid rib syndrome		PTCH1	9q22.32	AD	Multiple odontogenic keratocysts, mild mandibular prognathism[40]
Beckwith-Wiedemann syndrome		NSD1	5q35.2 to 5q35.3	AD	Macroglossia[41]
			11p15.5		
		H19	11p15.5		
		KCNQ1OT1	11p15.4		
		CDKN1C			
Caffey-Silverman syndrome		COL1A1	17q21.33	AD	Tender swelling of mandible[42]
Cowden's syndrome		PTEN	10q23.31	AD	Oral fibromas, xerostomia[43]
			10q22.3		
DiGeorge's syndrome		CATCH22	22q11.2	AD	Micrognathia, cleft lip/palate[44]
Epidermolysis bullosa simplex		KRT5	12q13.13	AD	Generalized blistering of oral cavity[45]
		KRT14	17q21.2		
McCune-Albright		GNAS	20q13.32	AD	Fibrous dysplasia of craniofacial bones[46]
Noonan syndrome		PTPN11	12q24.13	AD	High-arched palate, articulation difficulties, micrognathia less frequently mandibular cysts, which can mimic cherubism[47]
Osteogenesis imperfecta	IA	COL1A1	17q21.33	AD	Type IB, III and IV associated with dentinogenesis imperfects[48]
	IB				
	III	COL1A1/ COL1A2	17q21.33 7q21.3	AD and AR	
	IV	COL1A1/ COL1A2	17q21.33 7q21.3	AD/AR	
Pachyonychiacongenita	I	KRT6A	12q13.13	AD	Oral leukokeratosis[49]
		KRT16	17q21.2		
	II	KRT17			Oral leukokeratosis (less common than type I), natal teeth[50]
Peutz-Jeghers syndrome		STK11	19p13.3	AD	small, dark-colored spots on the lips, around and inside the mouth on buccal mucosa[51]
Retinoblastoma		RB1	13q14.1 to 13q14.2	AD	Large mouth with thin upper lip, cleft palate[7]
Stickler syndrome	I	COL2A1	12q13.11 to 12q13.2	AD	Micrognathia, midline clefting ranging from bifid uvula to cleft lip and palate[52]
	II	COL11A1	1p21		
	III	COL11A2	6p21.3		
Tooth agenesis		MSX1	4p16.2	AD	Hypodontia
		PAX9	14q13.3		Oligodontia
		AXIN2	17q23 to 17q24		Oligodontia associated with colorectal cancer[53]
		ED1	Xq13.1	X	Oligodontia[54]
Tuberous sclerosis complex	I	TSC1	9q34	AD	Pitted enamel, gingival fibromas, bony cysts[55]
	II	TSC2	16p13		
van der Woude syndrome		IRF 6	1q32 to 1q41	AD	Hypodontia, lip pits, cleft lip and palate[56]

Contd...

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Syndrome		*Gene*	*Chromosomal locus*	*Inheritance*	*Oral manifestations*
Waardenburg syndrome	I	PAX3	2q36.1	AD (few, type III and IV cases may be AR)	Cleft lip (rare)
	IIA	MITF, SNAI2 PAX3	3p14 to 3p13		
	III	SOX10, EDN3, or EDNRB	2q36.1		
	IVA		13q22.3		
Robinow syndrome				AD	Misaligned teeth, gingival hyperplasia, abnormal uvula and cleft lip and/or palate[17]
		ROR2	9q22	AR	
Ectodermal dysplasia	I	ED1	Xq13.1	XR	Conical or pegged teeth, hypodontia or complete anodontia and delayed eruption of permanent teeth[57]
	II	GJB6	13q12.11	AD	
Carpenter's syndrome	I	RAB 23	6p11.2	AR	Micrognathia/Retrognathia, high-arched/narrow palate, partial anodontia, malocclusion[58]
	II	MEGF8	19q13.2		
Chediak-Higashi syndrome		CHS1/ LYST	1q42.3	AR	Severe gingivitis and gingival hemorrhage and early tooth loss due to bone loss of alveoli, aphthous ulcer[59]
Bloom's syndrome		BLM	15q26.1	AR	Malar and mandibular hypoplasia[60]
Papillon-Lefevre syndrome		CTSC	11q14.2	AR	Early onset periodontitis and premature loss of deciduous as well as permanent dentition[61]
Werner syndrome		WRN	8p12	AR	Relatively stretched and thin lips, circumoral radial furrows[62]
Epidermolysis bullosa dystrophica		COL7A1	3p21.31	AR	Erosions, blisters, eventually depapillated tongue, ankyloglossia, microstomia and increased caries incidence[63]
Odontohypophosphatasia		ALPL	1p36.12	AD/AR	Premature exfoliation (incisors), reduced thickness of the dentin, enlarged pulp chambers of teeth, increased dental caries[64]
Bloch-Sulzberger syndrome		IKBKG	Xq28	XD	Partial anodontia, cone or peg-shaped teeth and delayed dentition[65]
Lesch-Nyhan syndrome		HPRT1	Xq26.1	XR	Self-mutilation in the form of lip biting[66]
Menkes syndrome		ATP7A	Xq21.1	XR	Delayed tooth eruption, high-arched palate[67]
Wiskott-Aldrich syndrome		WAS	Xp11.23	XR	Hemorrhage or petechial rash on oral mucosa[68]

neck, defects of the cervical and lumbar vertebrae, absence of the pubic symphysis and hypoplasia of the pelvis is common in females, flat feet (57%), knock knee deformity (28%) and scoliosis (18%) are found in children younger than 5 years of age, hearing loss and be prone to sinus and ear infections have also been reported in few cases.

Craniofacial features include delayed ossification of the cranial sutures and fontanels, and it may remain open throughout life, brachycephaly, a prominent forehead, hypertelorism, depressed nasal bridge, hypoplastic maxillary, lachrymal, nasal and zygomatic bones, frontal and parietal bossing, relative prognathism due to short, underdeveloped maxilla and the maxillary sinuses may be small or missing.

Oral Manifestations

Include delayed loss of the primary teeth, delayed appearance of the secondary teeth, peg-shaped teeth, malocclusion and supernumerary teeth, sometimes accompanied by follicular cysts and palate may be abnormally high, and occasionally, a cleft palate has been reported.[14]

Dentinogenesis Imperfecta

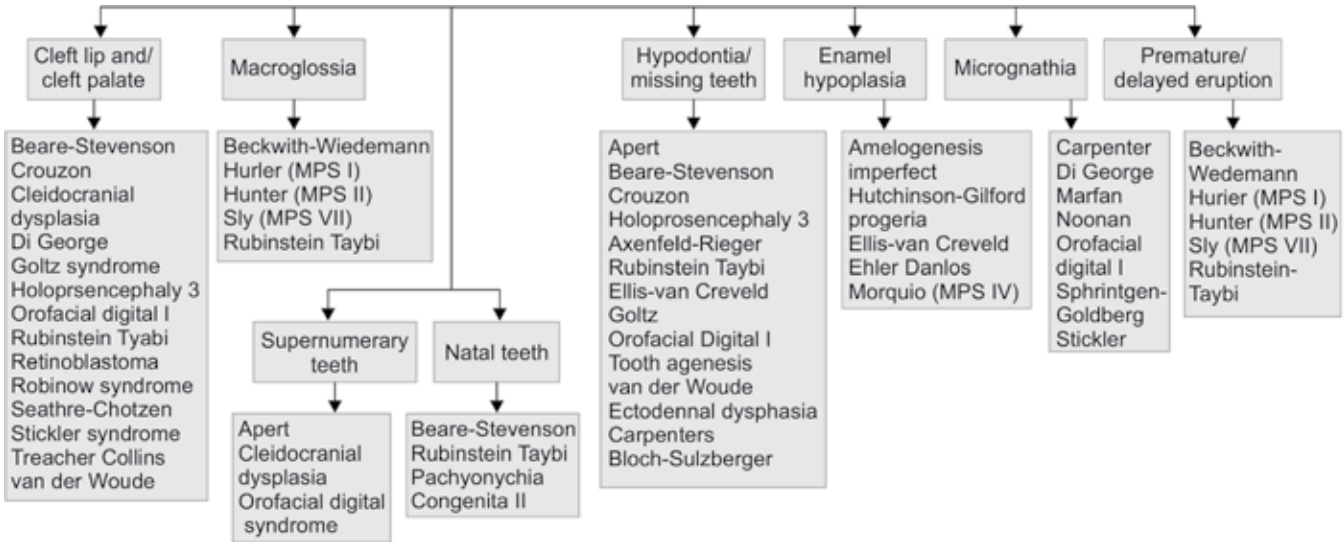
Dentinogenesis Imperfecta is an autosomal dominant inherited disorder with an incidence of 1 in 8,000. According to Shield's classification, it is of 3 types.

Type I

Type I occurs along with osteogenesis imperfecta. Defective genes are COL1A1 and COL1A2, located in the 17q21.33 and 7q22.1 chromosomal locus respectively.

Oral manifestations: Include amber translucent tooth color in both the dentitions primary teeth are affected most severely, followed by the permanent incisors and first molars, with the second and third molars being the least altered. Radiographically, the teeth have bulbous crowns, cervical constriction, thin roots, and early obliteration of the root

Flow Chart 2: Single gene disorders with common oral manifestations



canal and pulp chambers due to excessive dentin production. Periapical radiolucencies and root fractures are evident.

Type II

Also known as hereditary opalescent dentin. The features are caused by defect in DSPP located in 4q22.1 chromosomal locus.

Oral manifestations: They are similar to Type I affecting equally the primary and permanent dentition. Radiographically, pulp chamber obliteration can begin prior to tooth eruption.

Type III

Type III is the rare type of dentinogenesis imperfecta caused by mutations in DSPP gene located in 4q22.1 chromosomal locus.

Oral manifestations: Includes bell-shaped crowns, especially in the permanent dentition. In contrast to Types I and II, Type III involves teeth with shell-like appearance because of extremely thin dentin involving entire tooth or isolated areas on root, enlarged pulp space and multiple pulp exposures.[15]

Ehlers-Danlos Syndrome

The syndrome is named after Danish dermatologist Edward Ehlers (1901) and a French dermatologist Henri-Alexandre Danlos (1908). It is a connective tissue disorder with incidence of 1 per 20,000 to 100,000. The inheritance pattern is both autosomal dominant and recessive. The altered genes and their locations are ADAMTS2 (5qter), COL1A1 (17q21.33), COL1A2 (7q22.1), COL3A1 (2q31), COL5A1 (9q34.2–9q34.3), COL5A2 (2q14–2q32), PLOD1 (1p36.22), TNXB (6p21.3).

General and Craniofacial Features

Includes hypermobility of joints (shoulder, knee and temporomandibular) and spine, flat feet, scoliosis, excessive, generalized loosening of joints, muscular hypotonia, congenital bilateral hip subluxation, articular-muscular aches, skin lesions include excessively stretched, thin, gauzy and atrophic skin, easy bruising, delayed healing, significant scarring mainly located in areas exposed to pressure such as elbows, knees, chin, discoloration of the skin of the forehead, chin and legs, loss of elasticity of the skin and fascia.[16]

Oral Manifestations

Include extensive periodontal destruction, fragile gingival tissues, gingival bleeding, irregular dentin deposition, pulp stone formation and hypoplastic enamel.[17]

Hereditary Gingival Fibromatosis

Hereditary gingival fibromatosis is inherited mainly as an autosomal dominant disorder with the defective genes GINGF2, GINGF4, GINGF1 and GINGF3 located in 5q, 11p and 2p chromosomal locus respectively. It is characterized by spontaneous and progressive enlargement of the gingival tissues with the prevalence of 1 per 175,000 population and equal distribution in sexes. It can occur as syndromic or nonsyndromic forms. Few examples of syndromic forms are Zimmermann-Laband syndrome, Jones syndrome, Klippel-Trenaunay syndrome, Ramon syndrome, Rutherfurd syndrome and cross syndrome.

Oral Manifestations

The disorder can occur as nodular (localized, mostly seen in the maxillary tuberosity and molar area) and symmetric

forms (generalized, which is more common and both arches are equally affected). The affected gingival tissue is pink, usually shows exaggerated stippling, involving both free and attached gingival tissues, but extension beyond the muco-gingival junction is not observed. The side effects include speech problems, painful mastication, spacing, diastema, malocclusion and over-retention of primary teeth.[18]

Holoprosencephaly Type 3

Holoprosencephaly type 3 is a common neurological developmental defect, inherited as an autosomal dominant disorder and affecting around 1 in 10,000 live birth. It is characterized by failure of forebrain to divide into two cerebral hemispheres due to defect in SHH gene located in 7q36.3 chromosomal locus.

General and Craniofacial Features

Include microcephaly, hydrocephalus, synophrys, encephalocele, hypotelorism, hypertelorism, anophthalmia, microphthalmia, fused orbits, cyclopia, coloboma, epicanthal folds, ptosis, ethmocephaly, visual impairment, flat nose, philtrum pit, single nares (cebocephaly), septal defect/obstruction/deviation, pyriform sinus stenosis, proboscis, digit anomalies, club feet, cardiac defect, scoliosis and abnormal genitalia.

Oral Manifestations

Include maxillary agenesis, single maxillary central incisor, fused teeth, missing teeth, unilateral/bilateral/median cleft lip and unilateral/bilateral cleft palate.[19]

Hutchinson-Gilford Progeria Syndrome

Progeria was described by Jonathan Hutchinson (1886) and Hastings Gilford (1897). It is a rare autosomal dominant condition caused due to defect in LMNA gene located in 1q22 chromosomal locus. It is characterized by premature childhood onset aging with a prevalence of 1 in 4 million newborns.

General and Craniofacial Features

Include prenatal- and postnatal-growth delay, sparse hair/alopecia, prominent forehead, eyebrows/eyelashes, small face, thin nasal skin, convex nasal profile, absent ear lobule, high voice, lipodystrophy, narrow upper thorax, prominent abdomen, broadened finger tips, nail dystrophy, decreased mobility of joints and angina pectoris.

Oral Manifestations

Osteolysis of the mandible is more marked, which causes retrognathia, both the horizontal and ascending rami become smaller with age and the mandibular angle increases (often to about 150º), dental crowding, delayed eruption, dental caries, enamel hypoplasia, thin and small pulp chambers.[20]

Marfan's Syndrome

The syndrome was first noted by Antoine Bernard-Jean Marfan, a French pediatrician in the year 1896. It is a connective tissue disorder involving various organs, which include ocular, skeletal, cardiovascular, pulmonary, cutaneous and neurological defects. Pattern of inheritance is autosomal dominant with high penetrance. Defective gene caused by promoter mutations include FBN1 and TGFBR2 located in the 10q2 to 10q26 chromosomal locus. The incidence of 1 per each 5,000/9,800 individuals without any gender or ethnic distinction has been found.

General and Craniofacial Features

The skeletal defects include disproportioned overgrowth of long bones, pectus excavatum, scoliosis, articular hypermobility and flat foot may be presented. The cardiovascular features include the dilatation and dissection of the ascending aorta. The ocular symptoms manifests as dislocation of the lens, enophthalmos and sometimes as cataracts or glaucoma. A narrow cranium with dolichocephalic features, malar hypoplasia and down-slanting palpebral fissures are the prominent facial features. The temporomandibular defects are due to articular deformation and ligament hyperlaxity, which may cause pain during mastication, opening click or articular dislocation during wide mouth opening.

Oral Manifestations

The hard tissue defects include high-arched palate, retrognathia or micrognathia, posterior crossbite, crowding, increased overjet, open bite, flat molars hypoplastic teeth, disproportionate roots and pulp stones. The caries incidence and gingival and calculus index has an increased score on account of the dental defects.[21]

Neurofibromatosis I/Von Recklinghausen's Disease

A neurofibroma is a benign tumor arising from the Schwann cells and perineural fibroblast. Neurofibromatosis I is caused due to mutations in NF1 gene located in 17q11.2 chromosomal locus. The mutation leads to increased cell proliferation and tumor formation. It is a common genetic disorder with a prevalence rate of 1 in 3,000 newborns. It has an autosomal dominant inheritance pattern with complete penetrance and variable expression.

General and Craniofacial Features

Include café au lait spots (more than 6), inguinal and axillary freckles (Crowe´s sign), multiple skin neurofibromas

(mainly localized and plexiform), angiomas, osteolytic defects, kyphoscoliosis or pseudoarthrosis, iris hamartoma, acoustic neuoma, central nervous system tumors (glioma, glioblastoma), macrocephaly and mental retardation (up to 40% of cases) can also be found.

Oral Manifestations

Oral features are seen in 66 to 72% of the cases, 50% cases shows lengthening of fungiform papillae, 25% of cases present with oral neurofibromas in both soft and hard oral tissues (most commonly tongue), gingival neurofibromas may cause dental malposition or impaction, also radiological findings may include mandibular channel, mandibular foramen and mental foramen widening.[22]

Axenfeld-Rieger Syndrome

The syndrome was first described by Axenfeld in the year 1920. It is an autosomal dominant disorder involving multiple organ systems with a prevalence of 1 in 200,000. The various manifestations of the syndrome is a result of mutations in PITX2 and FOXC4 genes located in 4q25 and 6p25 chromosomal locus respectively. Most common causes of the altered genes are frameshift, nonsense and missense mutations.

General and Craniofacial Features

The ocular features include strabismus, hypertelorism, glaucoma; cardiovascular features include truncus arteriosus, mitral valve disease with ruptured chordae, tricuspid valve disease, pulmonic valve stenosis, bicuspid aortic valve, aortic valve stenosis, tetralogy of Fallot or atrial septal defects including an association with interatrial aneurysm. Joint abnormalities and umbilical or inguinal hernia is also reported. Craniofacial features include midface hypoplasia, a broad flat nasal root, maxillary and occasionally mandibular hypoplasia, short philtrum, thin upper lip and larger everted lower lip.

Oral Manifestations

Microdontia, hypodontia, oligodontia, underdevelopment of the premaxillary area, missing maxillary deciduous and permanent incisors and second premolars, crowns of the anterior teeth can be conical or peg-shaped, roots may be shortened, thickened frenulum, gingival attachments may be reduced and enamel may be hypoplastic resulting in poor dental health.[23]

Rubinstein–Taybi Syndrome

The syndrome was described by Rubinstein and Taybi in 1963. It is characterized by short stature, broad thumbs and toes, and facial abnormalities. It is an uncommon condition with an estimated prevalence of 1 in 100,000 to 125,000 newborns. It is caused due to mutations in the CREBBP gene located in 16p13.3 chromosomal locus, which is responsible for fetal cell growth and division.

General and Craniofacial Features

General features include absent or extra kidneys, posterior urethral valve, abnormal shape of the bladder, hypospadias, tumors like nasopharyngeal rhabdomyosarcoma, intraspinal neurilemmoma, neuroblastoma, pheochromocytoma and acute leukemia, and developmental defects of the thyroid gland, double transverse palmar crease or a single transverse crease and loop carpal pattern, mental retardation, patent ductus arteriosus and respiratory infections in infancy has been reported. Craniofacial features include antimongoloid slant, beaked nose, microcephaly, hypertelorism, abnormal ears in position, deviated nasal septum, thin upper lip, enlarged tonsils, high-arched eyebrow and strabismus.

Oral Manifestations

Includes microstomia, micro/retrognathia, highly arched and narrow palate, wide alveolar ridges, bifid uvula, submucous palatal cleft, natal teeth, hypodontia, supernumerary, double primary tooth, double permanent tooth, talon cusps, screwdriver incisors, elongation of the upper central incisors and extracusps on the primary molars, demarcated enamel opacities and hypoplasia, white tips of cusps on the first permanent molars, and white lines on the upper central incisors, enamel wear, bruxism, crowding, crossbite and bifid tongue, macroglossia and short lingual frenum.[24]

Treacher Collins Syndrome

The syndrome was first described by Dr E Treacher Collins in 1900. It is also known as mandibular dysostosis. It is an autosomal dominant disorder affecting derivatives of first and second pharyngeal arches with a prevalence of 1 in 40,000 to 1 in 70,000. The defective gene is TCOF1 located in 5q31.3 to q33.3 chromosomal locus, which causes defects in formation, proliferation, migration and differentiation of the neural crest cells, which is proposed to be the etiology of the syndrome.

General and Craniofacial Features

Includes antimongoloid slant, coloboma and hypoplasia of lower eyelids and lateral canthi, hypertelorism, partial loss of eyelid cilia, external ear, auditory canal and ossicular deformities with conductive hearing loss, nasal deformity leading to compromised respiration, hypoplasia of malar bones and lateral aspect of orbital bone, sleep apnea and sudden death in infants.

Oral Manifestations

Includes microstomia, hypoplasia of maxilla and mandible leading to variable effects on the TMJ, malocclusion, anterior open bite, steep occlusal plane, high-arched palate and cleft palate with or without cleft lip.[25]

Ellis-Van Creveld Syndrome

Ellis-van Creveld syndrome (EVC) is a rare autosomal recessive skeletal dysplasia with approximately 150 reported cases in literature till date. It was described by R Ellis (1940) and S van Crefeld (1968) and is characterized by short ribs, short limbs, postaxial polydactyly and dysplastic teeth and nails.

General and Craniofacial Features

Prenatal defects include narrow thorax, marked shortening of the long bones, hexadactyly of hands and feet, and cardiac defects. Abnormal features present at birth include disproportionate small stature with increasing severity from the proximal to distal portions of the limbs, and shortening of the middle and distal phalanges, polydactyly affecting hands and occasionally the feet, hidrotic ectodermal dysplasia mainly affecting the nails, hair and teeth and congenital heart malformations like single atrium, defects of the mitral and tricuspid valves, patent ductus, ventricular septal defect, atrial septal defect and hypoplastic left heart syndrome. Other features include strabismus, epi- and hypo-spadias, cryptorchidism, thoracic wall and pulmonary malformations. Skeletal defects include delayed bone maturation and bone fusion.

Oral Manifestation

Includes labiogingival adherences and gingival hypertrophy, labiogingival frenulum hypertrophy, accessory labiogingival frenula, serrated incisal margins, dental transposition, diastema, conical teeth, malocclusion, enamel hypoplasia and hypodontia, premature eruption of teeth and present at birth or premature exfoliation.[26]

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a part of lysosomal storage disease characterized by absence or faulty functioning of the lysosomal enzymes, which are essential for the breakdown of glycosaminoglycan molecules (formerly known as mucopolysaccharides).[17] They are mostly inherited as autosomal recessive disorders except MPS II, which has an X-linked recessive inheritance pattern. Different forms of MPS and their oral manifestations are detailed in Table 2.

Goltz's Syndrome/Focal Dermal Hypoplasia

The syndrome was described by Goltz in 1962. It is a rare X-linked dominant mesoectodermal disorder with unknown prevalence. It is characterized by focal total absence of dermal layer of skin. The manifestations of the syndrome are result of mutations in PORCN gene located in Xp11.23 chromosomal locus.

General and Craniofacial Features

Include skin pigmentations (asymmetrical linear streaks of atrophy and telangiectasia, which follows Blaschko's lines), generalized dryness and pruritus with soft reddish yellow nodules (fat herniation), raspberry-like papillomas occur on the lips, perineum, ears, fingers, toes, buccal mucosa and esophagus, nail absences or dystrophy with sparse and brittle hair are evident. Ocular lesions include microphthalmia with bilateral coloboma of the iris and ectopia lentis, strabismus, anophthalmia, keratoconus and corneal opacification. Skeletal defects include short stature, syndactyly, ectrodactyly, polydactyly, absence or hypoplasia of digits and even absence of an extremity, occasionally cervical rib, scoliosis, clavicular dysplasia and spina bifida occulta is seen. Radiologically, osteopathia striata of the long bones is characteristic. Craniofacial features include the presence of a small, rounded skull, triangular facial outline, pointed chin, protruding ears and asymmetrical ala nasi.

Oral Manifestations

Dental defects include prognathism, high-arched palate, cleft lip and palate, tooth agenesis, hypodontia, oligodontia, microdontia, enamel fragility and dysplasia, retarded eruption, irregular teeth spacing, malocclusion, hypertrophy of the gums, papillomas of the gums, tongue, palate and buccal mucosa may all take place.[32]

Orofacial Digital Syndrome I

Orofacial digital syndrome, also known as the Papillon-League-Psaume syndrome, is an X-linked dominant disorder with a prevalence of 1 out of 50,000 to 1 out of 250,000 live births. The manifestations are caused due to mutations in OFD1 gene located in Xp22.2 chromosomal locus.

General and Craniofacial Features

The craniofacial features include frontal bossing, facial asymmetry, ocular hypertelorism, strabismus, downslanting palpebral fissures aplasia of alar cartilage and broadened nasal bridge/root. Abnormalities of digits include syndactyly, brachydactyly and clinodactyly. Other features include dry,

Table 2: Types of mucopolysaccharidoses

MPS type	*Gene*	*Chromosomal locus*	*Inheritance*	*Oral manifestations*
Hurler syndrome (MPS I)	IDUA	4p16.3	AR	Hyperplastic gingiva, macroglossia, high-arched palate, short mandibular rami with abnormal condyles, spaced hypoplastic peg-shaped teeth with retarded eruption, localized dentigerous cyst-like radiolucencies[27]
Hunter's syndrome (MPS II)	XDS	Xq28	XR	Short and broad mandible, localized radiolucent lesions of the jaws, flattened temporomandibular joints; macroglossia, conical, peg-shaped teeth with generalized wide spacing, highly arched palate with flattened alveolar ridges, hyperplastic gingiva[28]
Sanfilippo syndrome (MPS III)	GNS, HGSNAT, NAGLU, SGSH	12q14 8p11.1 17q21 17q25.3	AR	The lower lip is often everted and thick, and the upper lip upturned with a protruding philtrum[29]
Morquio syndrome (MPS IV)	GALNS, GLB1	16q24.3 3p21.33	AR	Thin, rough and hypoplastic enamel, increased caries incidence[30]
Maroteaux-Lamy syndrome (MPS VI)	ARSB	5q14.1	AR	Enlarged tongue, gingival hypertrophy, delayed dental eruption[31]
Sly syndrome (MPS VII)	GUSB	7q11.21	AR	Macroglossia[7]

brittle hair, patches of hair loss and whiteheads, followed by the onset of kidney disease in adulthood.

Oral Manifestations

Includes micrognathia, cleft lip/palate, high-arched palate, oligodontia, supernumerary teeth, hyperplastic frenula and ankyloglossia.[33]

Rett Syndrome

The syndrome was first described by Rett in 1966. It is an inherited X-linked dominant neurodegenerative disorder with a prevalence of 1 in 12,000 to 1 in 15,000. The syndrome exclusively affects the females. The manifestations are caused due to mutations in MECP2 gene located in the Xq28 chromosomal locus.

General Manifestations

The major criterias for the diagnosis of the syndrome includes deceleration of head growth, loss of manual functional skills at age 0.5 to 2.5 years, stereotypic movements of the hands such as clenching, applause, washing movements or taking the hands to the mouth, social retraction, communication dysfunction, forgetting of learned words and cognitive disability, gait apraxia or failure to learn to walk. Supporting criteria include respiratory dysfunction like apneas, hyperventilation, sharp expulsion of air and saliva, aerophagia, sleep disturbances from infancy, abnormal muscle tone associated to dystonia, peripheral vasomotor alterations, scoliosis/kyphosis, retarded growth, small, hypotrophic and cold feet, small and thin hands.

Oral Manifestations

Include high-arched palate, open bite, mandibular lateralization, masseter hypertrophy, sialorrhea, digit sucking, oral breathing, tongue thrusting, bruxism, dental wear, gingivitis and dental caries.[34]

CONCLUSION

The 21st century is blessed by advanced technology in every aspect of medical science. It has become essential for all healthcare professionals to have a sound knowledge of genetic variations and its application in management of such patients. These newer technologies have aided in providing a remarkable insight of the genetic disorders at the DNA level and helped in the establishment of the molecular picture, which correlates with the clinical manifestations of these patients. In particular, identification of similar genetic defects with varied clinical features are being understood better now. This knowledge can serve beneficiary in risk assessment, carrier detection and prenatal identification of genetic defects with serious consequences. But the supreme goal from the therapeutic point of view would be to reach a stage wherein we are in a position to replace the defective genes. Soon the genetic screening and assays will prove to be more sensitive and rapid diagnostic tools, which will shape the future domain of medicine. Hence, the human genomics and proteomics along with bioinformatics and pharmacogenomics are the need of the hour for prevention, diagnosis and therapeutics in time ahead.

Further the single gene disorders with minor oral features are depicted in Table 1. In addition the common oral

presentations of various single gene disorders are enlisted in Flowchart 2.

GLOSSARY

Alleles: They are variants of a given DNA sequence at a particular location (locus) in the genome, oftenused to describe alternative forms of the same gene.[69]

Allelic heterogeneity: The existence of many different disease causing alleles at a given locus.

Autosome: Any chromosome other than a sex chromosomes.

Homozygote: An individual having identical alleles at a particular locus.

Heterozygote: An individual having two different alleles at a particular locus.

Hemizygous: Having only one copy of a gene or DNA sequence in diploid cells.

Compound Heterozygote: An individual with two different mutant alleles at a given locus.

Dominant: A trait that is expressed in a heterozygote.

Incompletely dominant: Describes a phenotype or trait when its severity in a hemizygous individual is intermediate between the homozygous and the normal or mutant allele.

Recessive: A trait that is expressed in a homozygote.

Genotype: The set of alleles that make up an individual's genetic make-up either overall, or at agiven locus.

Phenotype: The observable characteristics of a cell or organism resulting from its specific genotype.

Mutation: A change in the nucleotide sequence of the genome.

Consanguineous: It is used to describe couples who have one or more ancestors in common.

Pedigree: A graphical representation of a family tree.

Sibs: Brothers or sisters. An entire family of sibs is referred to as a sibship common symbols used in pedigrees.

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