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Review Article

Chromosomal and Multifactorial Genetic Disorders with Oral Manifestations

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Abstract:

The chromosomal disorders are individually rare, but collectively they are common whereas the multifactorial disorders are the most common form of genetic disorders. The chromosomal anomalies typically arise from alterations in the DNA containing chromosomal regions and can be reliably detected by karyotype analysis, whereas the multifactorial disorders demonstrate multi-gene as well as environmental interactions. Both the chromosomal and multifactorial disorders may manifest signs and symptoms such as a combination of birth defects, physical disabilities, challenging behavior and certain craniofacial defects as well, the knowledge of which can aid in a better patient management in everyday practice of dentistry.

Key Words: Chromosomes, multifactorial, polygenic, craniofacial, oral manifestations

Introduction

The chromosomes comprise of the DNA and proteins condensed in a compact structure with each species having its own representative number and form. Chromosomal disorders and syndromes often arise from numerical and structural defects of the chromosomes leading to varied manifestations, some of which also includes the craniofacial region. They can be associated with 50% of spontaneous abortions, 6% of stillbirths, around 5% of couples with a history of two or more miscarriages and with approximately 0.5% of newborns.[1]

The multifactorial inherited disorders are the commonest form of genetic disorders. They do not follow the Mendelian law of inheritance pattern, instead the multiple gene-gene interactions and multiple gene-environment interactions play a dynamic role in the pathogenesis and clinical manifestations of these disorders. Many of these chromosomal and multifactorial disorders present with characteristic oral manifestations and are discussed in this review.[2]

Chromosomes and Mutations

Normal chromosome

The origin of the word chromosome is from the Greek words "chromos" and "soma," meaning color and body respectively.[3] The accurate prediction of the human diploid chromosome number as 46 (i.e., males have 44 + XY and females have 44 + XX), was achieved by Tjio and Levan, which marked the beginning of a new era of human cytogenetics with its immense clinical applications with relation to chromosomal abnormalities.[4]

The basic elements of a chromosome includes a centromere, the chromosomal arms (short and long), telomeres and replication origins.[5] To understand the location of mutated genes in a chromosome locus, it is essential to understand the commonly used karyotyping terminologies. Karyotyping is the basic tool of cytogenetic studies and most commonly involves G banding staining technique. Karyotypes and structural alterations of chromosomes are described as short hand notations. The nomenclature includes arm, region, band and sub-band in order as seen in the Figure 1.

For example, Wolf–Hirschhorn syndrome (WHS) is caused due to deletion of 4p16.3 chromosomal portion, which represents the short arm of chromosome number 4, in region 1, band 6 and sub-band 3.[1]

Chromosomal abnormalities

Most chromosome abnormalities occur in the very initial stage of formation and fertilization of gametes, and therefore, the anomaly is present in every cell of the body. The chromosomal abnormalities can be due to alterations in number or structure of the chromosomes.

Numerical abnormalities

The usual causes of numerical abnormalities include the aneuploidy (which may be due to either nondisjunction or anaphase lag) and mosaicism as explained in Figures 2 and 3 respectively. The embryos conceived with autosomal monosomies and trisomies rarely survive due to greater loss of genetic material, whereas those involving sex chromosomes fairly survive with various developmental anomalies.[1,6]

Structural abnormalities

The structural abnormalities are mostly caused spontaneously by loss or rearrangement of the chromosomal material as seen in Figure 4.[1,6]

Chromosomal Disorders with Oral Manifestations (Flowchart 1)

9p trisomy syndrome

Individuals with trisomy 9p syndrome have well-defined phenotype with a female predilection. It was first described by Rethore *et al.* in 1970 and since then, more than 125 cases have been studied and reported in the medical literature. The phenotypic features of the syndrome varies depending upon the partial or complete trisomy of the short arm of chromosome number 9.

General features: Includes variable mental retardation, speech impairment, hypoplasia and dysplasia of terminal phalanges, single palmar crease, cyanosed hands and feet and dysplastic, claw-like nails.

Craniofacial features: Includes high, broad forehead, mild micro-brachycephaly, flat occiput large fontanelle and open metopic suture in childhood, small eyes, deep set in their sockets, horizontal or down-slanted palpebral fissures, mild hypertelorism, large, full nose with a globular tip and downturned nares.

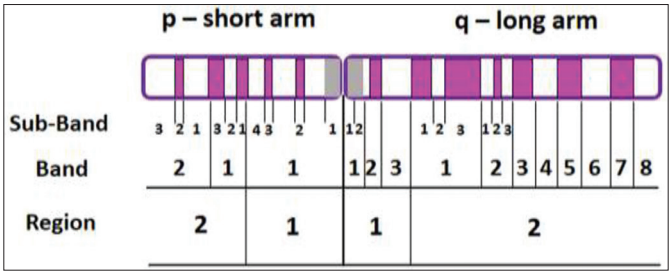


Figure 1: Banded karyotype nomenclature.

Oral manifestations: Includes large mouth with downturned angles, everted lower lip, micrognathia, narrow and high arched palate, microdontia, delayed eruption, mandibular retrognathism, dental crowding and few cases of cleft lip (CL) with or without cleft palate (CP) has also been reported.[7]

Down's Syndrome (DS)

DS is the most common chromosomal disorder caused due to trisomy of chromosome 21 thus, represents chromosomal numerical aberration defect. The incidence of DS is approximately 1 in 700 to 1 in 800 live births. It is mostly caused due to meiotic nondisjunction in 94% cases, unbalanced Robertsonian translocation in 4% cases and mosiacism in 2% cases.[1]

General features: Manifestations present during infancy includes learning disabilities, mental retardation with varying range of cognitive and other neurological dysfunctions and as well as cardiovascular defects. Skeletal features include broad and short extremities, clinodactyly and dysplasia of midphalanx of the fifth finger, dysplasia of pelvis, a wide gap between first and second toes and atlanto-occipital joint instability. Other features include ocular defects, transverse palmar crease, protuberant abdomen, hypogonadism and delayed puberty.

Craniofacial features: Includes brachycephaly, flat occiput, broad and short neck, flat facies with hypertelorism, prominent epicanthic skin folds, hypoplasia of the maxilla and outward slanting palpebral fissures.

Oral manifestations: Includes early onset severe periodontal disease (most significant oral health problem), lower prevalence of dental caries, delayed eruption of permanent teeth, malocclusion, congenitally missing and malformed teeth are common, microdontia, fissuring and thickening of lips, angular cheilitis, rarely CL or CP, macroglossia, fissured and protruding tongue, tongue thrust, bruxism and mouth breathing.[8-10]

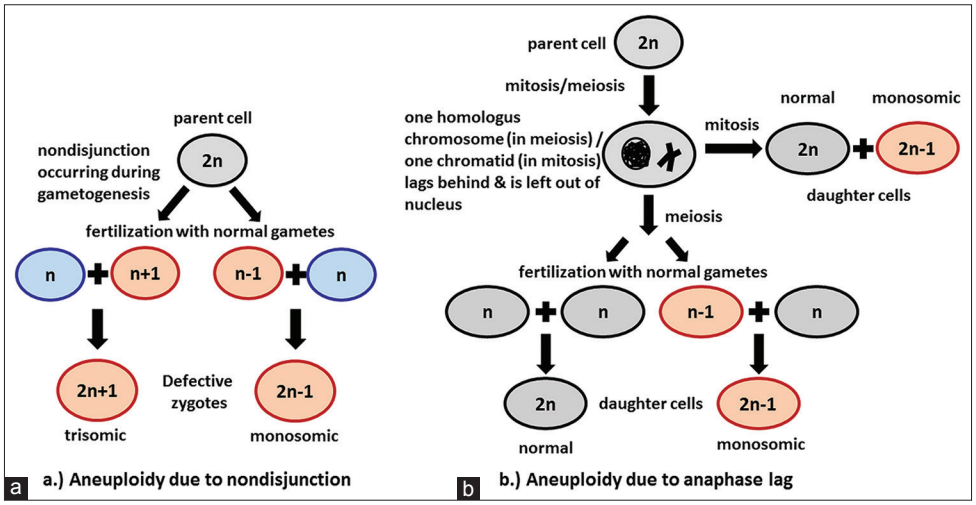


Figure 2: Numerical chromosomal abnormality due to aneuploidy. (a) Aneuploidy due to nondisjunction (b) Aneuploidy due to anaphase lag.

Edward's Syndrome (ES)

ES or trisomy 18 is the second most common trisomy after DS. It is also an example of numerical aberration. The ES is more common in females and frequency is approximately estimated to be 1 in 8,000 live births. The risk of ES increases with an increase in maternal age. Most commonly caused by unbalanced translocation involving a long arm of chromosome 18 and less commonly by mosiacism.[1]

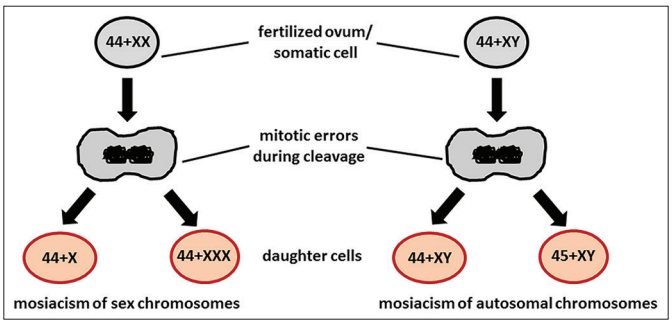


Figure 3: Numerical chromosomal abnormality due to mosiacism.

General features: Infantile features include low birth weight, clubbed feet and webbed or fused toes and severe mental retardation. Most infants do not survive beyond 2 weeks. Defects in digits, eyes, lungs, diaphragm, heart, and blood vessel formations are common and also kidneys may be malformed.

Craniofacial features: Includes microcephaly, low set and malformed ears.

Oral manifestations: Includes microstomia, micrognathia, retrognathia and narrow palate.[9,11]

Mosaic Trisomy 22

It is a rare chromosomal disorder. The manifestations are caused due to an extra copy of chromosome number 22. It has many types among which mosaic form is compatible with life

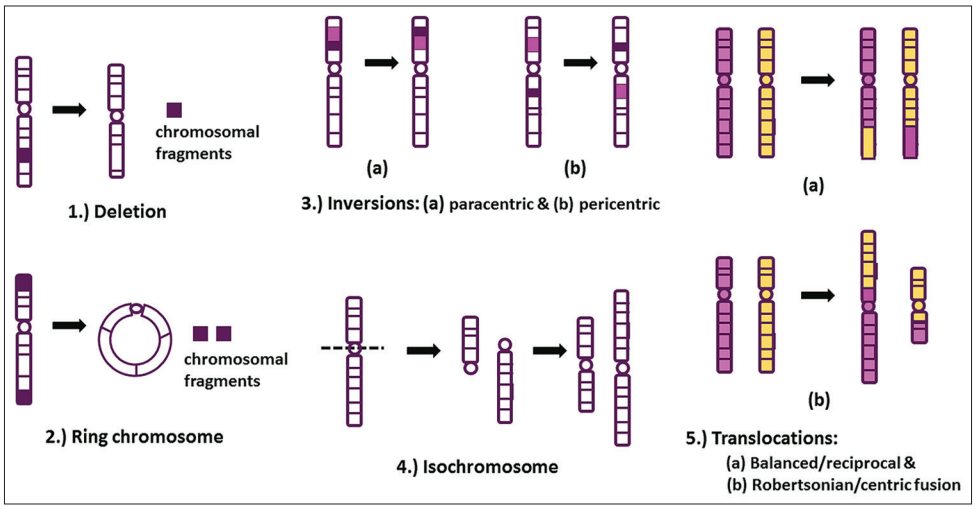
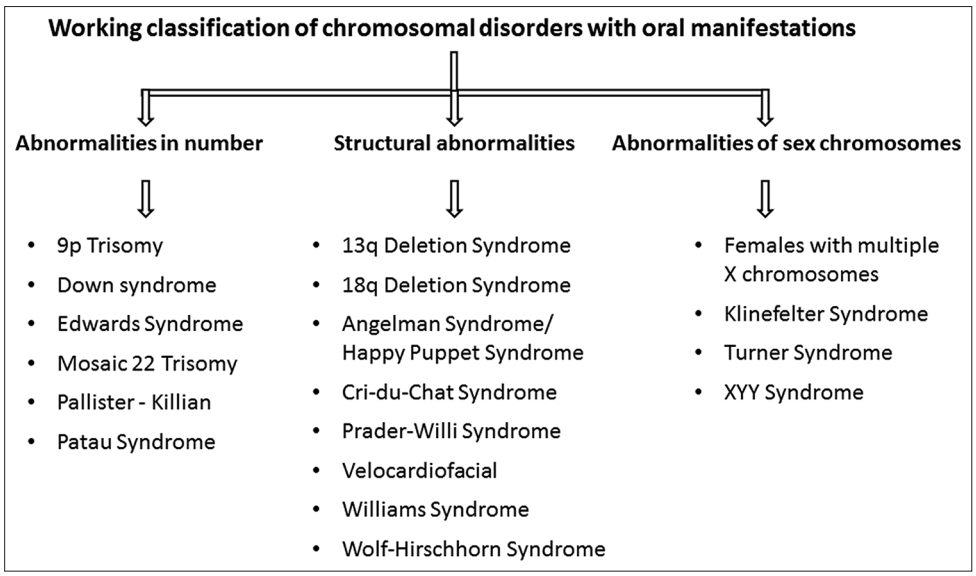


Figure 4: Structural chromosomal abnormalities.



Flowchart 1: Chromosomal disorders with oral manifestations.

and has prolonged survival of individuals whereas complete non-mosaic trisomy 22 is incompatible with life and causes spontaneous abortions.

General features: Include growth retardation, severe mental retardation, webbed neck, limb malformations and hypomelanosis of Ito. Also, congenital heart defects, hearing impairment and genital disorders such as cryptorchidism might also be present.

Craniofacial features: Include microcephaly, macrocephaly, prominent forehead, flat nasal bridge, preauricular pits, hypertelorism, bilateral epicanthic folds, and malformed low-set ears.

Oral manifestations: Micrognathia and CP.[12]

Pallister–Killian Syndrome (PKS)

PKS was first described in 1977 by Pallister *et al.* and independently reported in 1981 by Killian and Teschler-Nicola. It is an anomaly caused due to the tetrasomy of the chromosomal region 12p. Till date around 100 cases of PKS have been reported in the medical literature.

General features: Newborns and children with PKS often show hypotonia, profound mental and motor retardation along with a seizure disorder, frontotemporal alopecia, rarely diffuse hyper/depigmentation. Other features include skeletal malformation includes rhizomelic brachymelia, etc., ocular and cardiovascular abnormalities, congenital diaphragmatic defect and genital abnormalities.

Craniofacial features: Includes frontal bossing with a high frontal hairline, low set and dysplastic ears, hypertelorism, wide and flat nasal bridge, exophthalmos and shallow upper orbital ridges, upward slanting palpebral fissures, and inner epicanthic folds, small nose with upturned nares, the cheeks are full, and the philtrum is long and simple with a prominent upper lip and short neck with often webbed and excess nuchal skin.

Oral manifestations: Includes macrostomia with down turned corners, large mandible, high-arched palate and one case reported of CLCP and labial pits on lower lip.[1,9,13]

Patau Syndrome (PS)

PS was first described by Dr. Klaus Patau in 1960 and is least common of all the major autosomal trisomies. Incidence of PS is approximately 1 in 20,000 live births and increases with maternal age. Individuals with PS rarely survive, and approximately 70% die within first 6 months of their lives. It is an example of chromosomal numerical aberration, most commonly caused due to maternal meiotic, unbalanced Robertsonian translocation (20% cases) and rarely due to mosiacism.

General features: Birth defects include respiratory and heart defects, myelomeningocele, incomplete development of the optic and olfactory nerves usually accompany brain defects, ocular defects like holoprosencephaly, hearing disabilities and recurring ear infections. Other features include genital malformations, scoliosis, missing ribs, etc.

Craniofacial features: Includes microcephaly, flat facies, short nose and lips, increased area between upper lips and nose, bushy eyebrows and tumors on forehead are also typical.

Oral manifestations: Includes micrognathia, retrognathia, premaxillary agenesis, CP, and CL or both.[1,9]

13q Deletion Syndrome

13q deletion is a rare chromosomal disorder with approximately 120 cases reported in the medical literature. The deletion results in the formation of ring chromosome and based on the breakage point it can be categorized into three groups, group 1 (proximal to q32), group 2 (including q32) and group 3 (13q33 and 13q34). The incidence of 13q deletion syndrome is estimated to be 1 in 58,000 live births.

General features: Mental retardation, short neck with folds, congenital heart disease, imperforate anus, hypospadias (epispadias), undescended testes, bifid scrotum, pelvic girdle anomalies, foot and toe anomalies, absent thumb and short fourth and fifth finger.

Craniofacial features: Microcephaly, broad prominent nasal bridge, hypertelorism, microphthalmia, epicanthus, ptosis, colobomata, retinoblastoma, large low set (malformed) ears and facial asymmetry.

Oral manifestations: Includes micrognathia and protruding maxilla.[14,15]

18q Deletion Syndrome

18q deletion is one of the commonest syndromes with a prevalence of approximately 1 in 10,000 live births. It was first reported by de Grouchy *et al.* in 1964. The phenotypic features depend on the partial or total deletion of the long arm of chromosome number 18. The typical features are particularly related to the deletion in the 18q22.3 chromosomal region.

General features: Includes mental retardation, short stature, hypotonia, hearing impairment and feet deformities and endocrine disorders accompanied by autoimmunity.

Craniofacial features: Prominent facial features include microcephaly, deep set eyes, midface hypoplasia, carp-shaped mouth, a short palpebral fissure and outer ear abnormalities like preauricular pits and narrow or atretic external auditory canal.

Oral manifestations: Includes palatal defects.[16]

Angel Man Syndrome (AS)

The syndrome is named after its discoverer in 1950 but initially was referred as "Happy puppet syndrome." The most common cause of AS is micro deletions (70% cases), followed by uniparental disomy (5% cases) and abnormal methylation at 15q11-13 chromosomal loci due to imprinting mutations (4% cases). The prevalence of AS is around 1 in 10,000 live births.

General features: AS is characterized by severe mental retardation, lack of speech, EEG abnormalities, ataxia and stiff, atactic gait, developmental delay, aggressive behaviors, prolonged episodes of inappropriate laughter and episodes of seizures.

Craniofacial features: Typical facial features include microcephaly and deeply set eyes.

Oral manifestations: Include macrostomia, maxillary hypoplasia, mandibular prognathism protruding tongue and widely spaced teeth.[1,9]

Cri Du Chat Syndrome (CdCs)

CdCS is one of the relatively rare and earliest described syndromes. It is also known as "5p syndrome" and "cat-cry syndrome". The characteristic high-pitched, cat-like cry has been localized to chromosome 5p15.3. 90% cases of CdCS is caused due to *de novo* deletions of the p arm of chromosome number 5 and the remaining 10% is caused from an unbalanced familial translocations. The incidence of this syndrome is 1 in 50,000 live births.

General features: It is characterized by a high-pitched "cat-like" cry, delayed development, difficulty with language and mental retardation. Symptoms vary from one individual to the other based on different sizes and locations of deletions in chromosome 5p. Most common symptoms include behavioral problems, lower cognitive functioning, hearing impairments and scoliosis, and a small percentage of them may be born with serious organ defects.

Craniofacial features: Distinctive facial features of CdCS include microcephaly, broad nasal bridge and widely spaced eyes.

Oral manifestations: Includes micrognathia, malocclusion, especially overjet and CLCP.[1,9]

Prader–Willi Syndrome

The Prader–Willi syndrome (PWS) was first reported in 1956 and named after endocrinologists Prader, Labhart and Willi, who were first to report this syndrome. It is an example of structural abnormality of the chromosome resulting from paternal deletions on chromosome 15. The most common cause of PWS is microdeletions (70% cases), followed by uniparental disomy (30% cases) and abnormal methylation at 15q11-13 chromosomal loci due to imprinting mutations (1% cases). PWS has equal gender predilection with a prevalence of 1 in 12,000–15,000.

General features: Includes mainly increased risk of experiencing emotional, behavioural and cognitive impairment. Early symptoms include diminished fetal activity, profound poor muscle tone, underdeveloped sex organs, retarded bone age and delayed developmental milestones.

Oral manifestations: Includes dental caries, enamel hypoplasia, microdontia, malocclusion, heavy calculus, decreased salivation viscous, bubbly saliva, gingivitis, fish-like mouth with triangular shaped upper lip and arched palate.[1,9]

Velocardiofacial Syndrome (VCFS)

VCFS is derived from the Latin words "velum" which refers to palate, "cardia" referring to the heart and "facies" referring to the face. It is an example of chromosome microdeletion but can also result from simple deletion, translocation, ring chromosome, and less common structural changes affecting the long arm of chromosome 22, specifically the region containing the SHANK3 gene. The disorder occurs with equal frequency in males and females and affects about 1 in 2000 to 1 in 4000 newborns approximately.

General features: The syndrome manifests a number of psychiatric illnesses, including attention deficit disorder, schizophrenia and bipolar disorder, learning impairments, developmental delays, heart problems, eye problems, middle ear infections, immune system problems, low calcium, scoliosis and bone abnormalities in the neck or upper back.

Craniofacial features: The typical facial features include elongated faces, almond-shaped eyes, long eyelashes, full cheeks, wide or bulbous nose and unusual ears. Velopharyngeal insufficiency occurs in about 70% of patients with VCFS because of CP resulting in platybasia, hypotrophy of adenoid, enlarged tonsils, hypotonia, and abnormal pharyngeal muscles.

Oral manifestations: Includes CP usually of the soft palate.[1,9]

Williams Syndrome (WS)

WS is a rare neurodevelopmental condition associated with microdeletion of multiple adjacent genes at chromosome number 7. Among all, the deletion of elastin gene (ELN) plays a vital role in the development of cardiovascular defects. The deletion of other genes lead to the varied neurological manifestations of this syndrome. The incidence of WS is reported to be 1 in 20,000 to 1 in 50,000.

General features: Early childhood features include failure to thrive, developmental delay, congenital heart diseases, colic, umbilical hernia, inguinal hernia, esotropia, chronic otitis media, joint limitation, kyphosis, scoliosis, renal abnormalities, and hypercalcemia. Adulthood features mainly include urinary

tract infection, peptic ulcer, cholelithiasis and gastro-intestinal diverticulitis.

Craniofacial features: Include dolichocephaly, bitemporal depressions, facial asymmetry, flat mala, full cheeks, periorbital fullness, full nasal tip, depressed nasal bridge and long philtrum.

Oral manifestations: Includes hypodontia, microdontia, invagination of maxillary incisors, small and slender roots, pulp stones, increased space between teeth, enamel hypoplasia, a high prevalence of dental caries and malocclusion.[17]

WHS

WHS was first described by Hirschorn and Cooper in 1961 and later it was associated with deletions in the 4p (4p16.3) chromosomal region. Majority of the cases are caused due to de novo deletions and the remaining 10% is caused from an unbalanced translocation. Deletions that do not exceed 3.5 MB, average of 5-18 MB and more than 22-25 MB is frequently correlated with a mild, recognizable and severe phenotype respectively. The WHS affects females more frequently with an estimated occurrence of 1 in 20,000 to 1 in 50,000 births.

General features: The common features include growth and mental retardation along with midline fusion defects. Children with WHS show varied cognitive-behavioral profiles, seizures and sleeping disorders. In addition, poor muscle development, malformations of digits, chest and spine, urinary and genital organs have been reported.

Craniofacial features: Characteristic facial features include a prominent forehead, wide set eyes and broad beaked nose, collectively described as "Greek warrior helmet."

Oral manifestations: Includes CL or CP.[1,9,18]

Females with Multiple X Chromosomes

The syndrome exclusively affects the females. The syndrome is caused due to the presence of extra copies of X chromosomes or due to mosaicism leading to only few cells with multiple X chromosomes. The prevalence is approximately 1 in 1,000 females.

General features: No unusual physical features are notes. Some cases show increased the risk of learning disabilities and delayed development of speech, motor and language skills, hypotonia, and behavioral and emotional difficulties.[20]

Craniofacial manifestations: Includes broad flat nose, hypertelorism and epicanthus.

Oral manifestations: Includes resemblance to features of DS and prominent jaws.[2]

Turner Syndrome (TS)

TS is an X chromosome related disorder wherein one of the two X chromosomes normally found in women is missing or incomplete. Approximately 50% of TS patients have 45, X0 karyotype, around 30% are mosaics and others have X chromosome related abnormalities like isochromosomes, short-arm deletions and ring chromosomes. TS alters development in females only, and its prevalence is in about in 1 in 8,000 female babies. The incidence of TS is not dependent on maternal age and in about 75% of cases the paternal X chromosome is missing.

General features: The affected females are typically unable to conceive. Other common findings include a webbed neck with folds of skin, skeletal abnormalities, scoliosis, minor eye problems, middle ear infections, increased risk of heart defects, kidney problems, osteoporosis, thyroid problems and cataracts.

Craniofacial features: Facial features include minor dysmorphic face, small chin and curved upper lip.

Oral manifestations: Includes micrognathia, premature eruption of permanent molars, narrow maxilla, high arched palate and malocclusion.[1,9]

Klinefelter Syndrome (KS)

KS, also known as an XXY syndrome, results from extra X chromosome in males. About 10% these cases results from mosaicism. The prevalence of KS is approximately 1 in 1000 newborn males.

General features: Individuals with KS seldom know about their condition until they reach puberty. KS has also been associated with genital defects in males, an increased risk of breast cancer, extra-gonadal germ cell tumor, infertility, lung disease, osteoporosis and varicose veins, autoimmune disorders, learning disabilities and also some show an array of motor problems.

Oral manifestations: Includes maxillary and mandibular prognathism, mandibular prognathism being more common, permanent tooth crowns larger than usual and taurodontism.[1,9,19]

XYY Syndrome

The XYY syndrome exclusively occurs in males. It is caused due to the presence of an extra Y chromosome in males, apart from the normal one X and one Y chromosome, and is represented as 47, XYY. It may be also caused due to mosiacism. The phenotypic effects in an individual with XYY mosaicism depends upon the proportion of XY to XYY cells.

General and craniofacial features: Majority of the individual with XYY syndrome appear normal and are rarely aware of the condition. The minor features mainly include

problems in speech and learning disabilities and behavioral problems like aggressive behavior and temper tantrums.

Oral manifestations: Few reported cases show larger deciduous and permanent teeth than average and shovel-shaped lateral incisors.[19,20]

Multifactorial Inherited Disorders

These are a group of complex human diseases caused by multiple genes with environmental factors and appear to cluster in families over multiple generations. Some of the selected examples that demonstrate multigene and multigene-environment interactions and that are of importance to oral health care providers are discussed below.[2,6]

Neural Tube Defect

The neural tube defects are commonly caused due to problems inclosure of the neural tube during the early developmental phases and may affect any part of the brain and spinal cord leading to varied clinical presentations.

General and craniofacial features: Includes anencephaly, spina bifida, variable degrees of lower extremity paralysis, bladder and bowel incontinence, secondary hydrocephaly sometimes present, sacral hairy patch or dimple, diastematomyelia, intradural/extradural lipoma, caudal regression syndrome, sacral agenesis, intellect may or may not be affected depending on presence or absence of hydrocephaly and anatomical defect in region of the vertebral column.

Oral manifestations: Includes high and narrow palate.[19]

CLCP

Non-syndromic CLCP results from complex multifactorial traits. Various studies have linked the etiology of CLCP to the regions in chromosome number 6 (6p23-24, 6p24.3 and 6p23), endothelin-1 (ET1) which encodes for vasoactive peptide, G-coupled endothelin receptor (ETA) which is expressed in neural crest-derived ectomesenchyme and transforming growth factor β3 gene on chromosome 14q24. Other controversial genes, still under research, related to non-syndromic CLCP include F13A, BCL-3 on chromosome 19 and RARA on chromosome 17. Environmental factors like maternal smoking and alcohol consumption has been also linked with development of non-syndromic clefting.[21]

Table 1: Summary of chromosomal disorders with major oral manifestations.

Syndrome	Chromosomal abnormality	Affected chromosome	Oral manifestations
9p Trisomy	Trisomy and mosiacism	9p	Macrostomia with downturned angles, everted lower lip, micrognathia, narrow high arched palate, microdontia, delayed eruption, mandibular retrognathism, dental crowding and others with or without CP
DS	Trisomy due to meiotic nondisjunction, unbalanced Robertsonian translocation and mosiacism (rarely)	21	Delay in eruption of permanent teeth, malocclusion, microdontia, angular and macroglossia
ES	Trisomy due to unbalanced translocation and mosiacism	18	Microstomia, micrognathia, retrognathia and narrow palate
Mosiac 22 Trisomy	Trisomy and mosiacism	22	Micrognathia and CP
Pallister–Killian	Tetrasomy	12p	Macrostomia with down turned corners, large mandible and high arched palate
PS	Trisomy due to maternal meiotic nondisjunction, unbalanced Robertsonian translocation and mosiacism (rarely)	13	Micrognathia, retrognathia, premaxillary agenesis, CP and CL or both
13q Deletion syndrome	Deletions	13q	Micrognathia and protruding maxilla
18q Deletion syndrome	Deletions	18q	Palatal defects
Angleman	Microdeletions, uniparental disomy and imprinting mutations	15	Macrostomia, maxillary hypoplasia, mandibular prognathism protruding tongue and widely spaced teeth
CdCs	*De novo* deletions and unbalanced familial translocations	5p	Micrognathia, malocclusion, and CLCP
PWS	Microdeletions and uniparental disomy	15	Enamel hypoplasia, microdontia, malocclusion, decreased salivation, gingivitis, fish-like mouth and arched palate
WS	Microdeletions	7	Hypodontia, microdontia, invagination of maxillary incisors, pulp stones, enamel hypoplasia and malocclusion
WHS	De novo deletions and unbalanced familial translocations	4p	CL or CP
VS	Microdeletion	22	CP of the soft palate
Females with multiple X chromosomes	Extra copy of X chromosome	X	Similar to DS
TS	Missing X chromosome and mosiacism	X	Micrognathia, premature eruption of permanent molars, narrow maxilla, high arched palate and malocclusion
KS	Extra copy of X chromosome and mosiacism	X	Maxillary and mandibular prognathism with taurodontism
XYY syndrome	Extra copy of Y chromosome and mosiacism	Y	Larger deciduous and permanent teeth and shovel shaped lateral incisors

DS: Down's syndrome, ES: Edward's syndrome, PS: Patau's syndrome, CdCs: Cri Du Chat syndrome, PWS: Prader-Willi syndrome, WS: William syndrome, WHS: Wolf–Hirschhorn syndrome, VS: Velocardiofacial syndrome, TS: Turner's syndrome, KS: Klinefelter syndrome, CLCP: Cleft lip and plate

Conclusion

The chromosomal and multifactorial inherited disorders have an enormous impact on the clinical and social life of the affected individuals. The phenotypic consequences of these disorders depend on the imbalance of involved parts of the genome along with the influence of environmental factors, maternal age and the likelihood of transmission of the defects to the next generation. Predicting such outcomes can be diagnostic dilemmas and an enormous challenge for genetic counseling, particularly in the prenatal setting. Nevertheless, all health professionals are required to understand that the knowledge of genetics should not be confined only to scientific literature, but extended in practising and improving the health care.

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