Chromosomal disorders and oro-dental defects – prenatal diagnosis

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Abstract

Genetic disorders can be classified as single gene inheritance, multifactorial inheritance, chromosome abnormalities and mitochondrial inheritance. Every congenital structural defect in the body represents an inborn error in morphogenesis and may affect one or more systems. Currently, craniofacial abnormalities can be detected by modern ultrasound examination as early as at 16 weeks of gestation. Several chromosomal disorders, numerical and structural as well, include oro-dental defects among their clinical symptomatology. The severity of these disorders vary widely from extremely severe to mild, but oral defects are present in all. Chromosomal disorders and syndromes often arise from numerical and structural defects of the chromosomes, leading to various manifestations, some of which also include the craniofacial region. Genetics and its understanding and applications enhance our ability to understand the growth and development of craniofacial structures, leading to the early intervention and prevention of disease onset. Knowledge of the genetic alterations that may cause oro-dental defects allows the genetic examination, the prenatal diagnosis and counselling of future parents with traits of oral cleft in the family.

Keywords: *oro-dental defects, prenatal diagnosis, chromosomal disorders*

Rezumat

Tulburările genetice pot fi clasificate ca moștenire genetică unică, moștenire multifactorială, anomalii cromozomiale sau moștenire mitocondrială. Fiecare defect congenital structural din organism reprezintă o eroare înnăscută în morfogeneză și poate afecta unul sau mai multe sisteme. În prezent, anomaliile craniofaciale pot fi detectate de examenul ultrasonografic modern încă de la 16 săptămâni de gestație. Mai multe tulburări cromozomiale, numerice și structurale, includ defecte orodentare prin simptomatologia lor clinică. Severitatea acestor tulburări variază foarte mult, de la extrem de severe la ușoare, dar defectele orale sunt prezente la toate. Tulburările și sindroamele cromozomiale apar adesea din defectele numerice și structurale ale cromozomilor, ceea ce conduce la manifestări variate, dintre care unele includ și regiunea craniofacială. Genetica și înțelegerea ei, precum și aplicațiile sale sporesc abilitatea noastră de a înțelege creșterea și dezvoltarea structurilor craniofaciale, conducând nu numai la o intervenție timpurie, ci și la prevenirea declanșării bolii. Cunoașterea modificărilor genetice care pot provoca defecte orodentare este posibilă datorită examinării genetice și diagnosticului prenatal și permite consilierea viitorilor părinți ce vor avea urmași cu despicături orale în familie.

Cuvinte-cheie: *defecte orodentare, diagnostic prenatal, tulburări cromozomiale*

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Anomaliile cromozomiale şi defectele orodentare – diagnosticul prenatal

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Background

Genetic disorders can be classified as single gene inheritance, multifactorial inheritance, chromosome abnormalities and mitochondrial inheritance.

The medical management of individuals with syndromes affecting craniofacial and dental structures is mostly accomplished by an interdisciplinary team from early childhood on.

Structural morphogenetic defects – definitions

Every congenital structural defect in the body represents an inborn error in morphogenesis and may affect one or more systems. In general, most congenital anomalies can be divided into four types (Figure 1)[(1)]:

a) Disruptions: a rare anomaly related to breakdown of the original normal foetal developmental process – e.g., craniofacial cleft resulting from amniotic bands.

b) Deformations: these occur secondary to mechanical forces, leading to anomalies of a lesser degree when compared to disruption – e.g., club foot, cleft palate, Pierre Robin sequence etc.

c) Malformations: a morphologic defect in an organ from an intrinsically abnormal developmental process – e.g., polydactyly, congenital heart anomalies, cleft lip etc.

d) Dysplasia: an abnormal growth or development of a specific tissue or organ.

Genetic changes

The chromosomal abnormalities can be due to alterations in the number or structure of the chromosomes.

The chromosomal anomalies typically arise from alterations in the DNA containing chromosomal regions and can be reliably detected by karyotype analysis[(1,2,3)].

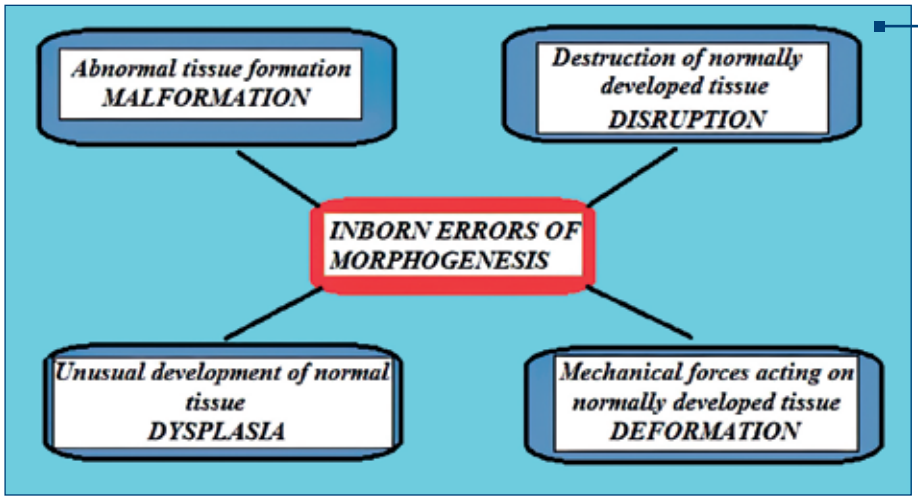

Figure 1. *Types of inborn errors of morphogenesis*[1]

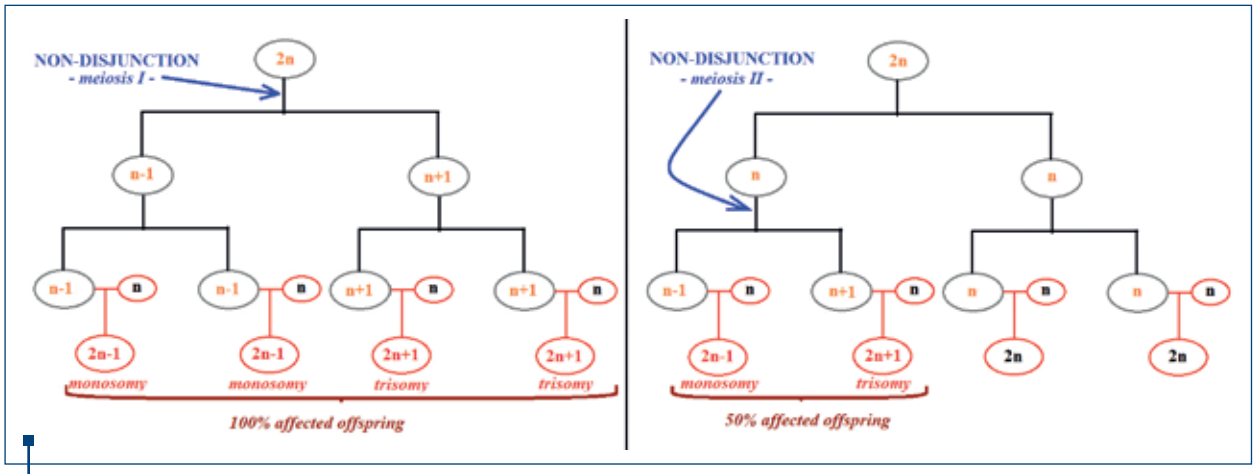

Figure 2. *Meiotic nondisjunction*[3]

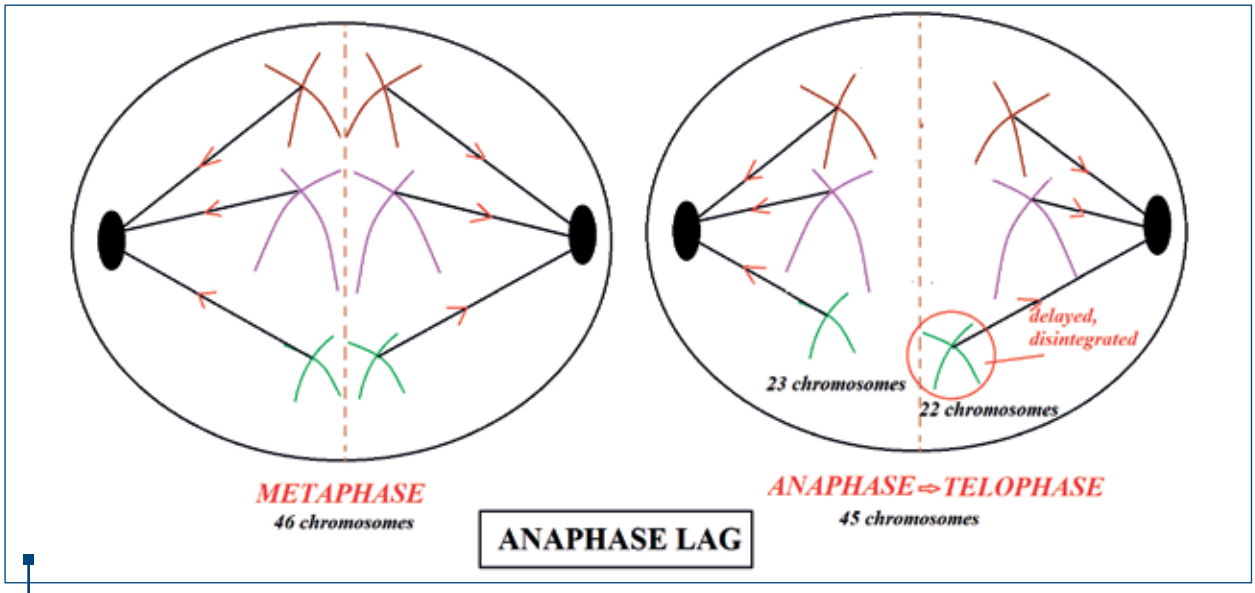

Figure 3. *Anaphase lag*[4]

Karyotyping is the basic tool of cytogenetic studies and most commonly involves G banding staining technique.

a) Numerical abnormalities

The most frequently reported numerical abnormalities are aneuploidies which may be due to either nondisjunction or anaphase lag (Figures 2 and 3)[3,4].

b) Structural chromosomal abnormalities

Structural abnormalities are mostly caused spontaneously by loss or rearrangement of the chromosomal material[4].

Chromosomal disorders and syndromes often arise from numerical and structural defects of the chromosomes, leading to various manifestations, some of which also include the craniofacial region.

Genetics and its understanding and applications enhance our ability to understand the growth and development of craniofacial structures, leading to the early intervention and prevention of disease onset[2,4-6]. Dental health caregivers should be aware of the technological and scientific improvements in the field of genetic testing and at the same time have ethical restraints over unrealistic expectations from it[2,7,8].

Several chromosomal disorders, numerical and structural as well, include oro-dental defects among their clinical symptomatology (Table 1)[10-50]. The severity of these disorders vary widely from extremely severe to mild, but oral defects are present in all.

Discussion

The development of novel clinical therapies for orofacial and dental pathological conditions depends very much on a detailed knowledge of the molecular and cellular processes that are involved in head formation.

c) Clinical relevance of genetic findings

Currently, craniofacial abnormalities can be detected by modern ultrasound examination as early as at 16 weeks of gestation[2,51]. In oral clefts, which are particularly relevant to clinical dentistry, the only therapy available for the closure of the cleft(s) is the surgical intervention. The identification of the molecular players and the unraveling of the genetic pathways that dictate palatogenesis and lip formation could offer new and exciting possibilities for the prevention and therapy of orofacial defects[1-8,51].

The knowledge of the genetic alterations that may cause oro-dental defects allows the genetic examination, prenatal diagnosis and the counseling of future parents with traits of oral cleft in the family.

Conclusions

The control of genetic diseases should be based on an integrated and comprehensive strategy combining the best possible treatment and prevention through community education, population screening, genetic counseling, and the availability of early diagnosis.

Genetic counseling will encompass legal and psychosocial management issues related to genetic screening, privacy and confidentiality, disclosure of unexpected and unwanted findings, and obligations to identify and communicate difficult issues. ■

Compliance with ethics requirements:

The authors declare no conflict of interests regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008, as well as the national law. The informed consent was obtained from the patient included in the study. No funding for this study.

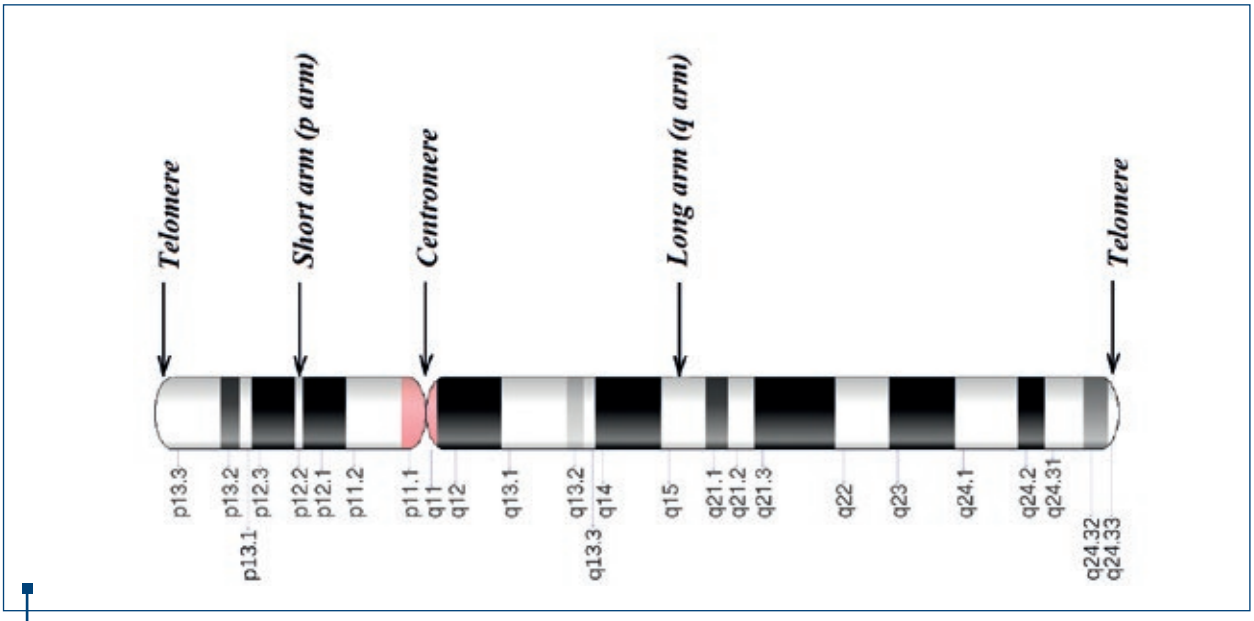

Figure 4. *Human chromosome morphology*[9]

Table 1 Chromosomal disorders with oro-dental defects

Syndrome	Clinical features	Genetic alteration
Down syndrome (10), (11), (12), (13)	Specific dysmorphic features with brachycephaly, epicanthic folds, upslanting palpebral fissures, shorter limbs, hypotonic muscles, learning disabilities, and physical growth retardation.	1-Trisomy-21 (95%): Not inherited 2-Mosaicism (3-4%): Not inherited 3-Translocation (1-2%): Inherited
Edward's syndrome (10), (11), (14), (15), (16)	Prominent occiput, small chin, narrow palpebral fissures, and mental delay.	Trisomy 18
Wolf-Hirschhorn Syndrome (10), (11), (17), (18), (19), (20)	Frontal bossing, high hairline, prominent glabella, short prominent philtrum, mental retardation, cleft lip and/or cleft palate.	Deletions of short arm of chromosome 4
Patau syndrome (10),(11), (21), (22)	Cleft lip and palate, broad nasal bridge, sloping forehead, mental retardation, microcephaly, occasional holoprosencephaly, microphthalmia.	Trisomy 13
Turner's syndrome (10), (11), (23), (24), (25)	Minor dysmorphic face, narrow maxilla, small chin, curved upper lip, straight lower lip, prominent ears and neck webbing, premature eruption of permanent molars, high arched palate and malocclusion.	45,X (X monosomy)
9p trisomy (10), (26), (27), (28), (29)	Severe psychomotor retardation; short stature; microcephaly; genu valgum; kyphoscoliosis. Dysmorphic facial features included: maxillary prognathism; narrow high-arched palate; short philtrum; small low posterior dysplastic ears; and down slanting palpebral fissures. Supernumerary premolars and opalescent changes of the maxillary incisors might be part of the clinical features.	Trisomy 9p
13q deletion syndrome (10), (30), (31), (32)	Low birth weight and failure to thrive, short stature, severe delay in the acquisition of skills requiring the coordination of mental and muscular activity. Severe intellectual impairment is also present in most cases. Many infants with partial monosomy 13q may exhibit characteristic abnormalities of the head and facial (craniofacial) area such as microcephaly, flat nasal bridge, micrognathia with an abnormally prominent upper jaw (maxilla); protruding front teeth (incisors), large, low-set ears; and/or a short neck with abnormal skin folds (webbing).	Deletion of long arm of chromosome 13
18q deletion syndrome (10), (33), (34), (35), (36)	Characteristic features include short stature; mental retardation; poor muscle tone (hypotonia); malformations of the hands and feet. Characteristic craniofacial findings may include microcephaly, hypoplastic midfacial regions, deeply set eyes; a "carp-shaped" mouth; and/or relative protrusion of the lower jaw (mandibular prognathism). Some affected individuals may also have an incomplete closure (clefting) or unusual narrowness of the roof of the mouth (palate); and/or an abnormal groove in the upper lip (cleft lip).	Deletion of long arm of chromosome 18
Mosaic Trisomy 22 (10), (37), (38)	Growth retardation, severe mental retardation, webbed neck, limb malformations, 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 cleft palate.	Trisomy 22 mosaic
Velocardiofacial syndrome (10), (11), (39), (40), (41)	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 cleft palate resulting in platybasia, hypotrophy of adenoid, enlarged tonsils, hypotonia, and abnormal pharyngeal muscles. Oral manifestations include cleft palate usually of the soft palate.	Chromosomal 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

Table 1 Chromosomal disorders with oro-dental defects (cont.)

Syndrome	Clinical features	Genetic alteration
Williams syndrome (WS) (10), (11), (42), (42), (44)	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 gastrointestinal 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 include 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.	Microdeletion of multiple adjacent genes at chromosome 7
Cri Du Chat syndrome (10), (11), (45), (46), (47), (48)	It is characterized by a high-pitched "cat-like" cry, delayed development, difficulty with language and mental retardation. 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: microcephaly, broad nasal bridge and widely spaced eyes. Oral manifestations include micrognathia, malocclusion, especially overjet and cleft palate and lip.	Deletion of short arm of chromosome 5
Klinefelter syndrome (KS) (10), (11), (49), (50)	Genital defects in males, an increased risk of breast cancer, extragonadal germ cell tumor, infertility, lung disease, osteoporosis and varicose veins, autoimmune disorders, learning disabilities. Oral manifestation: maxillary and mandibular prognathism, mandibular prognathism being more common, permanent tooth crowns larger than usual and taurodontism.	47, XXY

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