Oral and Craniofacial Diseases & Disorders

Chapter 3

Genetics of Orofacial Clefts

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1. Introduction

Orofacial clefts, cleft of the lip (CL) with or without cleft palate (CP), are one of the commonest birth defects, and may be associated with other congenital anomalies [1, 2].

The National Institute of Dental and Craniofacial Research (NIDCR) estimates that in the United States a baby is born every hour with a craniofacial defect [3].

Genetics plays a very important role in normal craniofacial development, abnormal dental anomalies, and different dental diseases such as dental caries, periodontitis, and dental malocclusion [4].

Identification of the molecular genetic pathways that dictate palatogenesis and lip formation could offer new and exciting possibilities for the prevention and therapy of orofacial clefts [5 - 7].

2. Classification

International Classification of Diseases (ICD), defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive and hierarchical fashion [8].

According to ICD - World Health Organization's, orofacial clefts include:

I. CLEFT LIP

- Cleft lip, bilateral

- Cleft lip, median
- Cleft lip, unilateral
- Cleft lip unspecified

II. CLEFT PALATE

- Cleft hard palate
- Cleft soft palate
- Cleft hard palate with cleft soft palate
- Cleft uvula
- Cleft palate, unspecified

III. CLEFT PALATE WITH CLEFT LIP

- Cleft hard palate with bilateral cleft lip
- Cleft hard palate with unilateral cleft lip
- Cleft hard palate with cleft lip, unspecified
- Cleft soft palate with bilateral cleft lip
- Cleft soft palate with unilateral cleft lip
- Cleft soft palate with cleft lip, unspecified
- Cleft hard and soft palate with bilateral cleft lip
- Cleft hard and soft palate with unilateral cleft lip
- Cleft hard and soft palate with cleft lip, unspecified
- Unspecified cleft palate with bilateral cleft lip
- Unspecified cleft palate with unilateral cleft lip
- Cleft palate with cleft lip, unspecified

3. Genetics

The high familial aggregation rates, recurrence risks and elevated concordance rates in monozygous versus dizygous twins provide evidence for a strong genetic component in clefts

lip and palate [9].

- Clefts of the lip and palate have been of interest in the scientific literature since at least the 1700's, and currently represent one of the major success stories in applying modern molecular genetic techniques to a common, complex disorder [10].
- Cleft lip is a fissure in the upper lip that is due to failure of the left and right sides of the fetal lip tissue to fuse, an event that should take place by 35 days of fetal age [11].

Cleft lip includes: cheiloschisis, congenital fissure of lip, harelip and labium leporinum.

- Cleft palate (palatoschisis) is an opening of the hard palate (the bony front portion of the roof of the mouth) or the soft palate (the muscular non-bony region in the rear of the roof of the mouth [11].
- Associated dental abnormalities includes: supernumery teeth, dystrophic teeth, missing teeth and malocclusion.
- Cleft lip and cleft palate which can also occur together as cleft lip and palate, are variations of a type of clefting congenital deformity caused by abnormal facial development during gestation [12].

3.1. Etiology of cleft lip and cleft palate

Cleft lip and cleft palate is etiologically heterogeneous with both genetics and environmental contributions.

The major cause in development of non-syndromic cleft lip and palate has not been fully elucidated due to complex interaction between genetic and environmental risk factors [13].

- The most common risk factors reported were:

✓ Heredity (genetic predisposition)

✓ Maternal exposure to tobacco products, alcohols, radiation, some viral infections (Rubella virus), nutritional deficiencies, physiologic and traumatic stresses during development

✓ Defective vascular supply to the affected area

✓ Mechanical disturbances (tounge size may interfere)

✓ Effect of medications: Retinoic Acid, Phenytoin, Valproic Acid, Aminopterin, Cortison, Thalidomide, Anticancer drugs, etc.

✓ Syndrome associated cleft lip and cleft palate: Gorlin, Oculofaciocardiodental, Stickler,

Smith–Lemli–Opitz, Crouzon, Apert, Cornelia de Lange, Campomelic dysplasia, Pierre Robin, DiGeorge, Treacher Collins, Orofacialdigital type I [14, 15].

3.2. Genetic predisposition of cleft lip and cleft palate

- According to Fogh and Anderson less than 40% of cases of cleft lip with or without cleft palate are genetic in origin transmitted through a male sex linked recessive gene and less than 20% of isolated cleft palates are genetically determined.
- Two possible mode of transmission - by a single mutant gene (monogenic) producing large effect or by a number of genes (polygenic inheritance) producing small effect.
- Gene that involves in the process:

✓ TGFB3

✓ MSX1

✓ AP2

✓ IRF6

✓ FGFR1, etc. [14].

3.3. Genetics of non-syndromic cleft lip with or without cleft palate

Non syndromic orofacial clefts specifically non-syndromic cleft lip/palate are one of the most common craniofacial malformation among birth defects in human having multifactorial etiology with an incidence of 1:700/1000, [13] .

- Non-syndromic inheritance is multifactorial.
- Positive family history in 26% cases:

✓ Cleft lip with or without cleft palate:

− One Parent - 2%

− One Sibling - 4%

− Two Siblings - 9%

− One Parent + One Sibling - 15%

✓ Cleft Palate:

− One Parent - 7%

- One Sibling - 2%
- Two Siblings - 1%
- One Parent + One Sibling - 17%

✓ Know teratogens:

- Specific drugs, i.e. Phenitoin, Methotrexate, Sodium Valproate
- alcohol, cigarette smoking
- pesticides (Doxin), [16, 17].

3.4. Reported etiologies of non-syndromic cleft lip with or without cleft palate

Nonsyndromic cleft lip and palate (CL/P) is a common craniofacial malformation with a complex genetic component [18].

✓ Candidate cleft lip/palate genes:

- IRF6
- MTHFR
- TGFA
- SATB2
- MSX1
- PVRL1
- TGFB3
- CLPTM1
- TBX22 [19]

✓ Maternal risk factors:

- Smoking
- Alchoolism
- Obesity
- Gestational and Pregestational diabetes

- Age > 40 years
- Dietary deficiencies in vitamins and minerals: Folate or Zinc deficiency [18].

✓ Teratogens:

- Valproic Acid, Diphenylhydantoin, Retinoic Acid, Phenobarbital, Benzodiazepines, Corticosteroid therapy , oral hormones , multi-drug therapy
- Chemical solvents
- Pesticides, herbicides, insecticides, fungicides
- Occupation related (leather, shoemaking, healthcare), [20, 21].

3.5. Genetics of syndromic cleft lip with or without cleft palate

Mutations in single genes and chromosomal abnormalities are the most common mechanisms underlying syndromic cleft lip/palate [22]. More than 500 syndromes are associates with cleft lip with or without cleft palate as part of the phenotype.

✓ Inheried Syndromes:

- Sticklers Syndrome (autosomal dominant)
- Van der Woudes Syndrome (autosomal dominant)
- Velocardiofacial Syndrome or 22q11.2 Deletion Syndrome (autosomal dominant)
- Treacher Collins Syndrome (autosomal dominant)

✓ Chromosomal anomalies:

- Trisomy 13 (Patau syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 21 (Down syndrome)
- partial deletions and duplications of other chromosomes

✓ Non-Inheried Syndromes:

- Pierre Robin sequence (50% have a Sticklers syndrome/22q11), [16].

3.6. Recurrence risk

The estimate of recurrence risk in non-Mendelian disorders requires a reliable model of inheritance, a large unselected sample of affected subjects, and an accurate diagnostic procedure to obtain a sample as aetiologically homogeneous as possible [23].

Isolated cleft palate has been shown to have a strong genetic component based on its high recurrence rate in families of affected individuals [24] .

✓ The recurrence risk for a cleft for another child depends on the severity of the cleft and the presence or absence of a family history.

✓ Recurrence risk and offspring risk figures are available for isolated cleft lip and palate and isolated cleft palate, and take into account the severity of the malformation. If the cleft is associated with a known syndrome, the recurrence risk will depend on the genetics of the syndrome [25] .

✓ The recurrence risks for cleft lip/cleft palate caused by complex inheritance are higher in families with more than one affected and in cases with a more severe presentation [bilateral vs. unilateral, isolated cleft lip vs. cleft lip and cleft palate [26].

3. 7. Genetic counseling

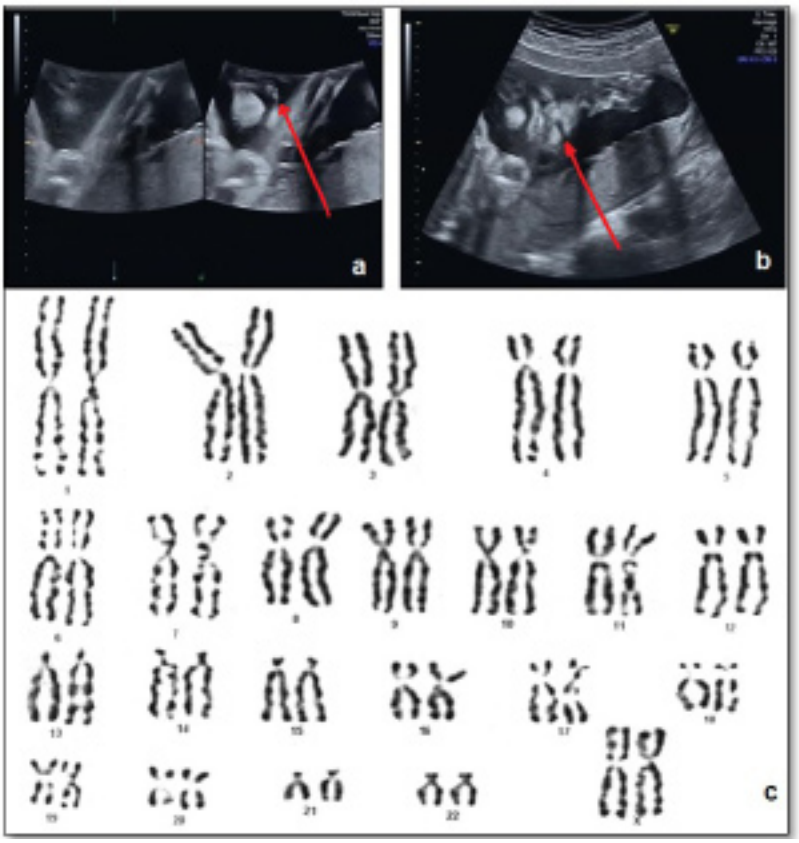
Children born with oral clefts have been shown to have higher mortality rates, especially in the presence of other birth defects [27, 28]. Care for this children is multidisciplinary and includes plastic surgery, nursing, maxillofacial surgery, otolaryngology, speech therapy, audiology, psychological counseling, genetic testing and counseling, dentistry, and orthodontics [24] .

✓ Genetic counselling for this condition is complex. Although most are considered multifactorial disorders (genes and environmental factors).

✓ Genetic counselling can identify high-risk families. The cleft team will refer those families where they think the child has a genetic syndrome. Talk to your cleft team about accessing the genetics service if you are worried. The recurrence risk is increased if the cleft is more severe [25] .

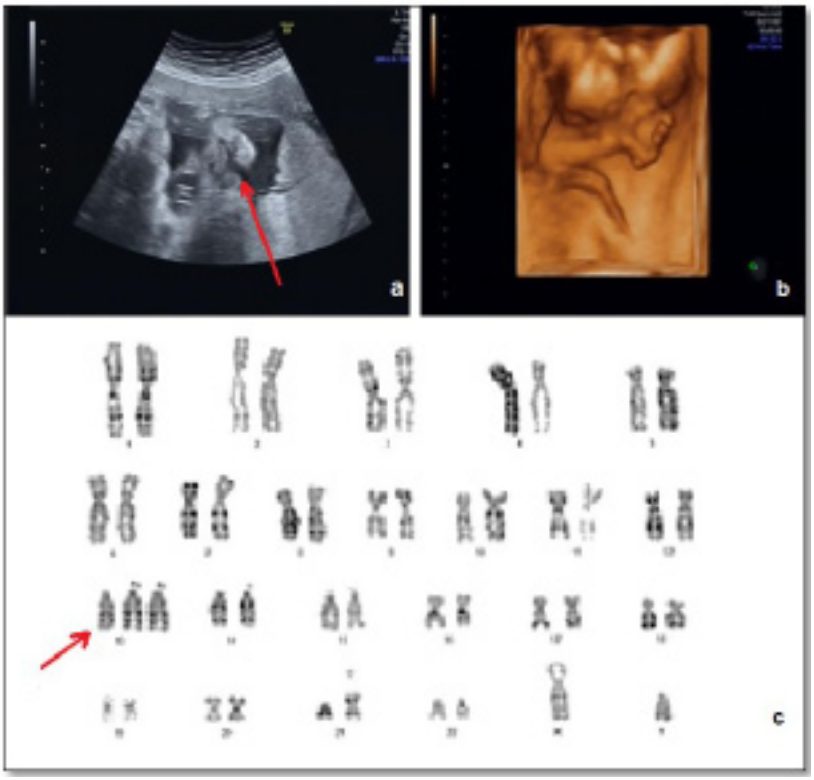
✓ Genetic testing for the nonsyndromic cases is only available under a research basis. With improved technology, cleft lip and cleft palate can sometimes be visualized on ultrasound. Clinical and/or research testing is available for some of the clefting syndromes [26].

✓ Currently, craniofacial abnormalities such as orofacial clefts, can be detected by prenatal modern ultrasound examination (**Figure 1** and **Figure 2**), [7, 29 - 31].



Images courtesy of Dr. Dinu-Florin Albu, [32].

Figure 1: Prenatal diagnosis of a fetus with non-syndromic cleft lip. Ultrasound examination: cleft lip (a, b); Karyotype 46, XX (c).



Images courtesy of Dr. Dinu-Florin Albu, [32].

Figure 2: Prenatal diagnosis of a fetus with syndromic cleft lip/palate: Patau syndrome. Ultrasound examination: cleft lip/palate (a), polydactyly (c, d); Anatomopathological examination (b); Karyotype 47, XY,+13 (e);

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