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Genetics And Its Association With The Developmental Anomalies Of

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ABSTRACT:

The embryonic head development, including the formation of dental structures, which is a complex and delicate process guided by specific genetic programs. The development of the face involves a coordinated complex series of embryonic events. Recognizable features of the human face develop around the 4th week of gestation and are closely related to cranial neural crest cells. Genetic changes and environmental factors can disturb the execution of these programs and result in abnormalities in the facial and dental structures. Orofacial clefts and hypodontia/ oligodontia are examples of such abnormalities frequently seen in dental clinics. This review article focuses on the mechanisms and genes involved in the formation of dental structures. The development dental pathological conditions depends very much on a detailed knowledge of the molecular and cellular processes that are involved in orofacial formation.

KEY WORDS: *Developmental disturbances of face, dental anomalies, orofacial malformation*

INTRODUCTION:

Disturbances in normal head development during embryogenesis manifest clinically as malformations that affect orofacial and dental structures. Fertilization is the fusion of male and female germ cells (the spermatozoa and ova, collectively called gametes) to form a zygote, which commences the formation of a new individual. Germ cells are required to have half as many chromosomes (the haploid number), so that on fertilization the original complement of 46 chromosomes will be reestablished in the new somatic cell. The process that produces germ cells with half the number of chromosomes of the somatic cell is called meiosis. Mitosis describes the division of somatic cells. Approximately 10% of all human malformations are caused by an alteration in a single gene. Such alterations are transmitted in several ways, of which two are of special importance. First, if the malformation results from autosomal dominant inheritance, the affected gene generally is inherited from only one parent[1]. The trait usually appears in every generation and can be transmitted by the affected parent to statistically half of the children. For example, abnormalities in the growth or fusion of the facial processes may result either in orofacial clefts or severe disorders such as holoprosencephaly, where the midline of the face "collapses". Similarly, tooth abnormalities are usually the result of disturbances in the "molecular dialogue" between the oral epithelium and the underlying mesenchyme during tooth development, which can result in tooth agenesis of varying severity with failure to form the correct number of teeth.[2]

PRENANTAL DEVELOPMENT:

The development of the face involves a coordinated complex series of embryonic events. Recognizable features of the human face develop around the 4th week of gestation and are closely related to cranial neural crest cells.[2] Prenatal development is divided into three successive phases. The first two, when combined, constitute the embryonic stage, and the third is the fetal stage. The forming individual is described as an embryo or fetus depending on its developmental stage. The first phase begins at fertilization and spans the first 4 weeks or so of

development. This phase involves largely cellular proliferation and migration, with some differentiation of cell populations. Few congenital defects result from this period of development because, if the perturbation is severe, the embryo is lost. The second phase spans the next 4 weeks of development and is characterized largely by the differentiation of all major external and internal structures (morphogenesis). The second phase is a particularly vulnerable period for the embryo because it involves many intricate embryologic processes; during this period, many recognized congenital defects develop. From the end of the second phase to term, further development is largely a matter of growth and maturation, and the embryo now is called a fetus[1]. For the development of the head a group of cells with stem cell properties, called cranial neural crest (CNC) cells, are of particular importance. These cells delaminate from the lateral ridges of the neural plate (which will form the neural tube) and then emigrate towards the developing branchial arches. Subgroups of cranial neural crest cells migrate towards specific areas where they intermingle with the existing population of mesodermal cells. The proliferation of the CNC cells is responsible for the budding of tissues around the future oral cavity.[1] Continuous neural crest stem cell proliferation leads to the formation of a single frontonasal process and of pairs of maxillary and mandibular processes. As development advances, all these processes join and fuse giving rise to the completed face. Thereafter, in both the maxillary and mandibular processes teeth will form. The facial processes fuse at different times; maxillary – 6 weeks, upper lip – 8 weeks and palate – 12 weeks.[3] The CNC cells will give rise to virtually all head structures with the exception of the muscles, which are formed by a mesodermal cell population. Further specification and organisation of the CNC cells into distinct elements (such as bones and teeth) takes place by means of a continuous "molecular dialogue" with the epithelium that covers the developing face and oral cavity. In this molecular "dialogue" the interaction between CNC cells and epithelium involves proteins that are products of specific genes. These proteins instruct cells to either divide or die (apoptosis), migrate/proliferate or differentiate into more specific cell types such as osteoblasts, odontoblasts, chondrocytes, etc. Molecular studies have shown that the growth, structure and pattern of the facial primordia is controlled by a series of complex interactions that involves many factors such as:

- fibroblast growth factors,
- sonic hedgehog proteins,
- bone morphogenetic proteins,
- homeobox genes Barx1 and Msx1,
- the distal-less homeobox (Dlx) genes,
- and local retinoic acid gradients

Orofacial and dental disorders result when mutations in the sequence of either a gene or a group of genes cause alterations to the expression or function of the encoded protein(s). Gene mutations, but also environmental factors, can affect the expression of genes or interfere with the normal function of their protein products.

GENES ASSOCIATED WITH REGIONALISED FACIAL FEATURES IN NORMAL HUMAN:

FACIAL STRUCTURES	GENES ASSOCIATED
Eye nasion distance	COL17A1, PAX3
Nose height	PRDM16
Inter-eye width	ALX3, GSTM2, GN13, HADC8, PAX3, TP63
Nasion, eye, zygoma, ear distance	C5orf50, PAX3, Intergenic, SOX9
Gonion-eye angle	OSR1-WDR35
Alae to nose tip	CHD8, CACNA2D3, PDDM16, ZNF219
Alae breadth	PAX1, PRDM16
Naso-labial angle	DCHS2, SUPT3H
Forehead	EYA4, GL13, RPS12, TBX15

Bridge of nose	EPHB3, DVL3, PAX3, RUNX2, SUPT3H
Eye shape	HOXD1-MTX2, WRDR27
Nasal sidewalls	PAX3, SUPT3H, Chr 1p32.1- intergenic
Mid-face height	PARK2,MBTPS1 (profile)
Alae	DCHS2, DVL3, EPHB3, KCTD15, SOX9
Nose prominence	CACNA2D3, DCHS2, ZNF219, CHD8
Lips	ACAD9, FREM1, HOXD cluster, RAB74
Mental fold	PKDCC
Chin	ASPM, DLX6, DYNC1L1, EDAR

The above mentioned are the genes associated for the regionalized facial features, any kind of mutation or disturbances in these gene could lead to anomalies related to the particular facial features.

MOLECULAR GENETICS IN DENTAL DEVELOPMENT.

The first sign of tooth development is a local thickening of oral epithelium, which subsequently invaginates into neural crest derived mesenchyme and forms a tooth bud. Subsequent epithelial folding and rapid cell proliferation result in first the cap, and then the bell stage of tooth morphogenesis. During the bell stage, the dentine producing odontoblasts and enamel secreting ameloblasts differentiate. Tooth development, like the development of all epithelial appendages, is regulated by inductive tissue interactions between the epithelium and mesenchyme. There is now increasing evidence that a number of different mesenchymal molecules and their receptors act as mediators of the epithelial-mesenchymal interactions during tooth development. Of the bone morphogenetic proteins (BMPs) 2, 4, and 7 mRNAs shift between the epithelium and mesenchyme in the regulation of tooth morphogenesis. The fibroblast growth factor (FGF) family have also been localized in epithelial and mesenchymal components of the tooth by immunohistochemistry; and in dental mesenchyme tooth development and shape is regulated by FGF8 and FGF9 via downstream factors MSX1 and PAX9.[3,4]

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DISORDERS IN TOOTH MORPHOGENESIS.

Advances in the field of molecular genetics have made great progress in the understanding of a number of dental anomalies with a genetic component.

RELATION BETWEEN GENETICS AND ENVIRONMENTAL FACTORS:

Facial morphology refers to a series of many different complex traits, each influenced by genetic and environmental factors. From the moment of conception, the parental environment can influence the development of the fetus. Facial development occurs very early at a time when the mother is not always aware that she is pregnant. The developing fetus may be subject to adverse environments at home, in the workplace or through lifestyle activities (smoking, alcohol and drug intake, allergens, paint, pest/weed control, heavy metals, cleaning, body products such as perfumes and creams). Many of these substances can cross the placenta (Naphthalene a volatile polycyclic aromatic hydrocarbon related to solvent emissions is present in household products and pesticides[5]. There is evidence to suggest that the effects of some of these substances can also continue post-natally through breast milk fed to the new-born[6]. Some of these early factors such as nictotine and alcohol may potentially influence on early neurological development. Indeed, there is evidence to suggest that high levels of prenatal alcohol exposure can influence facial morphology; individuals with fetal alcohol syndrome.[7]

CONCLUSION:

The face develops very early in gestation and facial development is closely related to the cranial neural crest cells. Disruption in early embryological development can lead to wide-ranging effects from subtle neurologic and facial features, which includes asymmetry, to significant impact on facial shape as characterized by a CL/P or in anomalies observed in craniofacial syndromes. Therefore a knowledge of the genetic processes involved in the formation of orofacial structures is important to understand any dental and orafacial anomalies.

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