REVIEW ARTICLE

MODERN DENTISTRY- A GENETIC PERSPECTIVE

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INTRODUCTION: The relative importance of environment and heredity in the development of various diseases and conditions is still a debatable topic. Most of the dental problems are found to have an interaction of these two factors. Many of the genetic disorders involve orofacial region and it is therefore of utmost importance for the dental surgeons to understand the normal development and mechanism involved in the development of abnormalities. We can consider hereditary head and neck pathology in a traditional sense as being either simple or complex consideration.

- Simple considerations are those resulting from single gene defect.
- Complex considerations are those which result from a collection of altered genes interacting with environmental influences.

Simple hereditary conditions:
Normal development and maintenance of the craniofacial complex is highly regulated at the molecular level. Odontogenesis can thus have simple gene disorders.

Congenitally missing teeth: Hypodontia is the most common simple hereditary trait affecting oral cavity with maxillary lateral and premolar being most commonly involved excluding 3rd molars. Several genetic mutations resulting in hypodontia have been identified. The missense mutation in MSX1 gene causes an autosomal dominant trait of variably missing lateral incisors, second premolars and 3rd molars. Mutation in PAX 9 gene has been associated with unusual pattern of hypodontia converting of missing mandibular incisors, molars premolars.

Complex hereditary Oral health condition: The 2 most common oral diseases that affect large segments of population are dental caries and periodontal disease.

Dental caries: Dental caries is considered an infectious disease; there are risk factors that are genetically determined including – pit and fissure morphology, enamel structure and composition, tooth eruption time, salivary flow and comparison, arch form, dental spacing, immunologic function and dietary preference. Studies of monozygotic twins suggest that approximately 50% of variance in dental caries can be attributed to hereditary factors. Understanding the human hereditary traits contributing to dental caries coupled with genetic knowledge of virulence of pathologic microorganisms involved will allow new diagnostic and novel therapeutic approaches to be applied for management of disease.

Periodontal pathology: The importance of a microbial etiology in periodontitis is well established and specific microbes appear to be associated with certain forms of periodontitis. In most cases microorganisms alone are not sufficient to cause disease. Significant data now supports an important role of hereditary susceptibility to a variety of types of periodontitis. Mutations of cathepsin C genes are responsible for

Disorder	Inheritance	Gene	Chromosomal map location
Hypodontia	Autosomal dominant	MS x 1	4p16
Hypodontia	Autosomal dominant	PA X 9	14q12 -q13
Anhidrotic ectodermal dysplasia	X linked	EDA 1	Xq12-q13
Anhidrotic ectodermal dysplasia	Autosomal recessive	EDA 2	2q11-q13
Anhidrotic ectodermal dysplasia	Autosomal dominant	EDA 3	2q11-q13
Condition	**Characteristics**	**Gene**	**Chromosomal map location**
Amelogenesis imperfecta 1 (AIH-1)	Thin enamel with rough surface	AMELX	Xp22mp
Amelogenesis imperfecta 2	Yellowish white teeth or opaque teeth	AMBN	4q11-q21
Amelogenesis Imperfecta 3 (AIH 3)	Hypoplastic enamel		Xq22-q28
Osteogenesis imperfecta	type III and IV associated dentinogenesis imperfecta	COLIA 1 & 2	17q21-q22
Dentinogenesis imperfecta	Opalescent dentin		4q31-q21
Cleidocranial dysplasia	Brachycephaly, delayed closure of fontanelles, wormian bone		6p21
Gardner's syndrome	Osteomas of frontal bone, maxilla, mandible odontomas, unerupted supernumerary teeth	APC	5q21

Papillion Lefere Syndrome, Haim Munk syndrome, and to some extent prepubertal periodontitis.

CHS-gene mutation causes Chediak Higashi syndrome and beta 2 integrin (a cell surface receptor) gene mutations are responsible for leukocyte adhesion deficiency type 1.

Genetic studies of aggressive forms of periodontitis suggest that susceptibility is inherited by genetic trait, but it is not clear how many genes may be involved in these non-syndrome forms of periodontitis.

Heredity also appears to play a significant role in most common form of chronic periodontitis. It is likely to result from the additive effect of multiple genes, which may each contribute to decrease susceptibility individually as well as through interactive effects with other gene products and through modulation by environmental factors.

Each individual gene polymorphism may contribute a relatively small part of susceptibility, none alone is sufficient to cause nor predictive of disease risk.

GENE THERAPY:

Impact of gene therapy on dentistry

1) Bone repair: An area of importance is bone repair subsequent to bony lesions. Ex vivo methods to transfer genes encoding bone morphogenetic proteins or BMPs –BMP-2 gene expressing stem cells increased formation of new blood vessels and new bone. Vivo gene transfer is carried out by using recombinant adenovirus Ad-BMP. The vector is administered directly to the osseous defect and expression of BMP-2 leads to repair of osseous defects.

In the future, it is likely that various genes soon will be able to regenerate bone and cell repair for periodontal and oral surgical applications.

2) Gene transfer to salivary glands: Salivary glands are excellent target sites of gene transfer. The original goal of developing gene transfer was to provide novel and effective therapies for patients who suffer from irreversible salivary gland dysfunction resulting from either irradiation of head and neck cancers or autoimmune damage occurring with Sjogren's syndrome. The idea in repair of damaged salivary gland was to insert a gene encoding water channel protein aquaporin – 1 or AQP-1 in converting non secretory cells to secretory cells. The second aspect is gene therapeutics. The idea here is to deliver gene product locally to treat disorders of mouth and upper G.I. The most successful one was in treating resistant candidial infection. The treatment lies with increase histatins 3 levels (a polypeptide secreted by salivary gland) that is a natural anticandidal polypeptide. Suitable gene transfer is carried out so that there is enhanced Histatins – 3 production and causing dentition of candida organism.

Similarly suitable gene therapy can make salivary gland act like an endocrine gland. Human growth hormone can be made available in the serum by secretion from acini of salivary gland directly to blood.

Using immunomodulation techniques can treat Sjogren's syndrome being autoimmune disease. Using gene transfer such as immunomodulation should be targeted, local delivery with selective tissue expres sion.

3) Pain: Managing or eliminating pain is a major part of dental practice. The use of gene transfer technology offers a potentially novel approach to manipulate specific localized biochemical pathways involved in pain generation. It may be particularly useful for managing chronic and intractable pain. Viral mediated transfer of genes encoding opiate peptide to peripheral and central neurons can lead to antinociceptive effects.

4) DNA vaccinations: Classical vaccination against dental caries and periodontal disease is now being replaced by directly delivering DNA in a plasmid. In 1999 extensive research was carried out using plasmid DNA encoding the porphyomonas gingivalis fimbrical gene. This gene led to production of fimbrial protein locally in salivary gland tissue of mice. With consequent production of sIgA the immunoglobulin could neutralize P.gingivalis and limit its ability in plaque formation. Furthermore any secreted fimbrial protein in saliva could bind to plaque and thereby inhibiting P.gingivalis to developing plaque.

5) Gene transfer to keratinocytes: There are several features that make epidermal and oral mucosal keratinocytes attractive for treating local tissue disorders and as a systemic gene therapeutic. That is because

- Monitoring is easy, because genetically modified tissue is accessible.
- Preclinical assessment is accurate since culture models are established.
- Expression of therapeutic genes can be achieved with the use of topically applied agents.
- Transplantation of keratinocytes sheets is an established medical procedure.
- Keratinocytes gene therapy is reversible because genetically modified tissue can be excised readily.

6) Head and neck cancer: The general strategy is to express a gene product that will result in cancer cell death. In normal cells, the tumor suppressive protein p53 monitors the integrity of the genome and responds to any DNA damage by inducing cell cycle arrest, to allow repair, or apoptosis if repair is impossible. In head and neck cancers p53 tumor suppressor gene mutation is between 45-70%. This aspect has lead to development of recombinant adenovirus that selectively replicates and kills p53 –deficient cells. The adenovirus replicate in cells with mutated p53 protein but spares cells with normal p53 protein.

The more recent studies have shown use of chemotherapy along with gene therapy and is highly successful in patient with recurrent and resistant tumor. Cis-platinum and 5-fluorouracil was used along with recombinant adenovirus therapy.

Most future gene therapy-based cancer treatment will be combined with conventional Rx. Such augmentive approaches, rather the gene transfer alone probably will be used to reduce tumor burden and help maintain quality of life in patients with head and neck cancer and other solid tumors.

Limitations of gene therapy: All said and done, we are just in initial stages of gene therapy. Infact, food and drug administration has put halts to some aspects of gene therapy trails on human beings using retrovirus. This became necessary after occurrence of leukemia in patient undergoing gene therapy for combined immunodeficiency. This move even though described as "temporary" is definitely a warning to all the proponents of gene therapy.

A high level committee of medicine observed that overzealous representation of medical gene therapy has obscured the nature of initial studies and has led to the widely held but mistaken perception that clinical gene therapy is already highly successful.

The committee was also criticized the biotechnology industry, noting that overzealous, uncritical reports of clinical results are used by industry to promote investment and perceived dominance.

Ethical, legal and social issues: The planners of US Human genome project recognized that information gained from mapping and sequencing, the human genome would have profound implications for individuals, families and society.

In many instances genetic testing creates situation where there is little precedent and no appropriate gold standard to compare results. For many scenario's it is difficult to know when to use a given genetic test, how to interpret results and how to fully and appropriately provide information for informed consent. Because of unique aspects of genetic testing, supplementary issues of privacy must be considered. Confidentiality takes an added dimension when applied to genetic testing. Genetic information can be intensely private, and generalization of this knowledge can have implications for patient's extended family as well as his/her assess to health care and employment.

Genetic information is not fundamentally different from other health information except that genes cannot typically be changed and hence can impart a determinate aspect of health. Genetic test results for one person may reveal genetic susceptibilities in parents, siblings of the patient.

References:

1)Gangane SD. Text book of Human Genetics.
2)Are we ready for clinical gene therapy? JADA. 1996;127: 396-398.
3)The Human genome, Implications for oral health and diseases and dental education. J Dental Pract Edu. May 2001.
4)The Genome projects: Implications for dental prac tice and education: J Dental Edu. May 2002
5)Genetics in dental practice: Social and ethical issues surrounding genetic testing: J Dental Edu. 2003: 549-562.
6)Impact of gene therapy on dentistry. JADA. 1995; 126: 179-189.
7)Impact of gene therapy on dentistry. Revisiting after 6 years .JADA 2002; 133: 38-44

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