REVIEW

Insights into the genetics of oral diseases – a scoping review

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ABSTRACT

With all recent developments and important clinical applications, this article presents an overview of the relation between genetics and oral health. Genetic factors determine the final structural development of oral tissues which have been supported by various investigations. Genes are the key factors that determine phenotypic traits and inheritance from parents to the offspring. Genetics is evolving rapidly with the identification of newer genetic etiologies of oral diseases. With more breakthroughs in technology, implementation of preventive strategies for the genetically predisposed individuals seems attainable. Identification of the causes of these disorders and their correction is not far off with the advancements in the field of genetics.

KEYWORDS: DNA Vaccination; Genes; oral cancer; oral health; traits

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INTRODUCTION

The frequently encountered issues today in dentistry are dental caries, periodontal diseases and malocclusion. There are many factors responsible for the occurrence of these disorders, one of them being genetic alterations. All these multifactorial aetiologies along with genetics and environment bring variability in the phenotype and genotype of an individual. Genetic disorders can be classified as shown in Table 1 [Kelly CG, et al.,1999; Chial H.,2008; Rieger R ,et al.,1968; Gabriel MS,et al.,2012].

Multifactorial trait Analysis

The variations between individuals having a common phenotypic trait (Vp) are due to both genetic variations (Vg) and environmental variations (Ve) i.e., Vp = Vg + Ve. These genetic variations are the cumulative effects of all genes favoring that trait i.e., additive component (Va), due to dominant component (Vd) and epistatic component (Vi), formulated as Vg = Va + Vd + Vi. The environmental variations are due to the common environmental component shared by a family (Vec) and the specific environment component shared by an individual (Vew). Heritability estimates help us to know the percentage of certain traits passed on from parent to offspring. They need to be interpreted with discretion as a single population has been taken under study facing similar environmental influences at that given time [Fisher RA.,1918].

Genetic Epidemiology

"A science which deals with the etiology, distribution, and control of disease in groups of relatives and with inherited causes of disease in populations" – given by Newton Morton [Morton, N. E.,1982]. This includes:

Table 1: Classification of genetic disorders

Disorders	Monogenic Inheritance	Polygenic Inheritance	Chromosomal Abnormality	Mitochondrial Inheritance
	Result of single mutative gene.	Result of combination of environmental factors and mutation in multiple genes	Result due to defective cell division leading to numerical as well as structural abnormalities	Result due to mutation in the non-chromosomal DNA of mitochondria
E.g.	Autosomal dominant: Amelogeneis Imperfecta etc.	Cleft lip with or without cleft palate	Trisomy 21, Trisomy 13, Trisomy 18	Leigh syndrome
	Autosomal Recessive: Oligodontia, Hypodontia etc.	Oral Cancer, Alzheimer	Klinefelter's Syndrome (XXY)	MELAS (Type of dementia)

	X linked: Cleft Palate, Duchene muscular dystrophy		Turner's syndrome (45X)	Leber's hereditary optic atrophy

Familial Aggregation Studies

Family aggregation is the clustering of certain traits, behavior or disorders within a family. Common genes, environmental exposures, and similar socio-economic influences are responsible for familial aggregation [Griffiths AJ,et al., 2000].

Complex Segregation Analysis (CSA)

The technique within genetic epidemiology to decide whether there is evidence that a major gene underlies the distribution of a given phenotypic trait. CSA helps to differentiate that a certain trait is inherited in Mendelian dominant, recessive, or co-dominant way. CSA uses only phenotypic information using the help of pedigree charts [Jarvik G.,1998].

Linkage Analysis

Is a genetic method that searches for specific gene location within the genome. As it is difficult to collect large familial pedigree data, this creates an obstacle to establish the genetic basis of dental disorders [Griffiths AJ,et al.,2000].

Twin studies

Twin studies help to unfold the influence of environment and genetics on traits and phenotypes. It is done by comparing identical (monozygous) twins and non-identical (dizygous) twins. The variable in monozygous twin studies is associated with environmental factors while in dizygous twin studies they are environmental as well as genetic factors [Grant C. Townsend,et al.,1998].

Genetics and Dental Caries

Dental caries is the most common disease of modern civilization. Sofaer reviewed the genetic basis for dental caries (Soafer, 1993). Genes allocate around 35 – 55% of caries phenotypic variation in the permanent dentition [Sofaer JA.,1993]. Studies and investigations done on inter-racial breeding have proved no genetic effect on the DMFT index [Schull WJ, Neel JV.,1965] which reveals that recessive genes do not play a major role in susceptibility to caries. Twin studies suggested that heredity plays a role in the incidence of caries. The Minnesota Study of Twins Reared Apart (MSTRA) [Grant C. Townsend ,et al.,1998] made a breakthrough in understanding the inheritable nature of caries. The genes laminin 5, Beta 4 – integrin, and type XVII collagen have the potential to alter the relationship of ameloblast to the developing enamel extracellular matrix and thus lead to a primary defect in the enamel hard tissue [Wright JT,et al.,1993;Wright JT,et al.,1994]. Variations in a protein sequence may lead to host immune response, salivary interacting factors, increased enamel porosity and decreased mineral content, etc. causing high dental caries risk [Shuler CF.,2001; Bretz WA,et al.,2003]. With the help of advanced genetic engineering production of transgenic strains of S. mutants devoid of decay causing gene and helps in caries prevention [Wang X,et al., 2012]. Specifically, targeted antimicrobial peptides (STAMPs) engineered to target S. mutants are helpful in caries prevention [Baker JL,et al., 2019].

Genetics and periodontal diseases

Periodontal diseases have multifactorial etiologies depending upon the host and environmental factors. Inherited diseases, genetic syndromes, familial studies have shown a major role of heredity and genetics in the periodontal health. Various

studies have suggested that localized juvenile periodontitis can be X-linked dominant, autosomal recessive, or autosomal dominant. It is observed that class I and II HLA antigens A9, A28, BW15 and DR4 are associated with the early onset of periodontal disease [Reinholdt J,et al.,1977; Katz J,et al.,1987; Shapira L, et al.,1994]. Ehlers Danlos syndrome types IV, VII and IX linked with early onset periodontitis may result in gingival overgrowth and periodontal destruction [Byers PH, Holbrook KA.,1990]. Catalase removes hydrogen peroxide but Acatalasia [Delgado WA, Calderon R.,1979] being a monogenetic condition inhibits the production of catalase thus adverse effects of hydrogen peroxide like gingival necrosis and severe bone destruction are seen. *ANRIL*, *COX2*, and *IL10* genes are related to aggressive periodontitis [Kornman KS, Polverini PJ., 2014]. "Deep" and "wide" analytical approaches are used for the identification of novel genetic locus which encodes regulatory cytokine interleukin 37 (IL 37) [Divaris K.,2019].

Genetics and Malocclusion

Dental occlusion is based on the interaction between multiple factors such as tooth size, arch size, shape, number and arrangement of teeth, size and relationships of jaws and influences soft tissues including lips, cheeks, and tongue. In 1960, Garn Lewis and Poleacheek [Patel DP, Gupta B,et al.,2012] studied the developmental stages of 1st and 2nd molars in two sets of triplets, thus concluding that dental development is genetically determined. Many other studies have suggested that heredity is an important factor in malocclusion.

Genetics and Craniofacial Development

Various studies have made fruitful points towards the relationship between craniofacial development and morphology with genetics. According to Smith and Bailit, these three major affect modes affect craniofacial development [Smith RJ, Bailit HL.,1977]:

A) Modes of inheritance

Popularly known Hapsburg jaw seen in Austrian royal family proves that occlusion has strong familial and hereditary relations.

B) Admixture and inbreeding effects have a direct relation with malocclusion.

C) The X and Y chromosomes

The X chromosome determines the enamel thickness while the Y chromosome determines both enamel and dentin. X and Y chromosomes have an influence over craniofacial development. Klinefelter's 47, XXY males show prognathism [Brown T, Alvesalo L,et al.,1993] while 45, X females show retrognathism [Peltomaki T, Alvesalo L,et al.,1989], crossbite, large maxillary overjet, open bite [Laine T, Alvesalo L,et al.,1986]. All the above point towards the X-chromosome affecting the morphology of the cranium. Amelogenin [Lau EC,et al.,1989] is the protein secreted by ameloblast. Amelogenin, the gene which is located on both X and Y chromosome although being predominant in X chromosome links to disorders such as Amelogenesis Imperfecta. Craniofacial protein development 1 (CFDP1) has been shown to function as a high order chromatin organizer in human cells [Messina G,et al.,2017].

Genetics and Cleft lip, Cleft palate

The prevalence of cleft lip, cleft palate is 1 in 500 in Asian populations, 1 in 800 to 1000 in Caucasian and the lowest in African population, i.e. 1 in 2500. The incidence of cleft lip and cleft palate are due to chromosomal disorders or might be due to multifactorial inception. Out of these, 70% are non-syndromic and 30% are syndromic [Schutte BC, Murray JC.,1999]. Some of the syndromic forms are;

a) Autosomal dominant syndrome e.g. cleidocranial dysostosis, Teacher Collins.

b) Autosomal recessive syndrome e.g. Cerebro Costo mandibular, Robert syndrome.

c) X linked inheritance e.g. orofacial digital

d) Chromosomal disorders e.g. Trisomy 13, Trisomy 18.

Kids and siblings of affected individuals are at way more risk than the general population [Schutte BC, Murray JC.,1999]. Methylation of CDH1 gene and deficiency of histone deacetylase4 (HDAC4) is associated with the phenotypical appearance of orofacial cleft [Alvizi L,et al.,2017].

Genetics and Oral Cancer

Association between biomarkers, stages of dysplasia and their progression to oral cancer is complex and requires the amalgamation of multiple variables. These variables are as follows [C. Seethalakshmi.,2013]:

1) Aneuploidy

About 68% of human solid tumors are aneuploid. Aneuploidy [Diwakar N,et al.,2005] may be due to gene dose imbalance, lack of TSGs, a gain of tumor-promoting genes, and oncogenes.

2) miRNA

Studies have found that many miRNA (micro RNA) sequences may act as tumor-suppressing genes and oncogenes, and thus affect the translation of the target mRNA.

3) Loss of Heterozygosity (LOH) and Allelic Imbalance (AI)

Loss of Heterozygosity studies is useful in locating TSGs. These TSGs encode proteins that negatively regulate cell growth. AI is the difference in the expression between two alleles of a given gene. Though LOH studies are helpful, AI studies are more accurate. It has been found that AI at 3p and 9p may cause genetic destruction in malignant lesions.

4) Epigenetic events and proto-oncogene

Mutations in the proto-oncogenes such as GSTM1 and GSTT1 or CYP cause hereditary instability in oral cancer. Modification of DNA and histones which are not present in the DNA sequence are still heritable changes known as epigenetic events [Egger G,et al.,2004].

5) The p53 family and Rb family

P53 family [Vousden KH, Lane DP.,2007] includes p53, p63, p73, p21, and p27. Genomic instability and accumulation of additional genetic alterations are due to the loss of p53 function which diminishes the control of cell cycle arrest and apoptosis, thus reducing the cell ability to act during a stressful situation such as DNA damage, hypoxia, and oncogene activation. p53 is the most commonly affected gene in oral cancer. Rb gene [Todd R,et al.,2002] is the first identified TSG and alteration in the Rb pathway may cause an oncogenic effect.

6) Cancer predisposition syndromes

Werner' syndrome, Bloom's syndrome, Fanconi's anemia, or disorders like Ataxia-telangiectasia.

Precision therapeutic options helped the prevention and treatment of squamous cell carcinoma by understanding of the activation of P13K/mTOR pathway in squamous cell carcinoma [D'Silva NJ, Gutkind JS.,2019]. The inhibition of PD-1 by immunotherapeutic agents shows constant antitumor activity in oral cancer [M.E. Ryan, C.H. Fox.,2019].

RECENT ADVANCES IN GENETICS

DNA Vaccination

DNA vaccination is a recent technology helpful in defense mechanism against diseases by injecting genetically engineered plasmid DNA which encodes antigenic proteins, thus producing protein expression intracellularly. DNA vaccines are much more potent and helpful than regular vaccines as they influence protective cytotoxic T-cells responses along with helper T-cells and humoral immune response [Alarcon JB,et al.,1999].

Biochips

Biochips are miniature laboratories which can perform hundreds to thousands of biochemical

reactions and thus ensure quick diagnosis of diseases. For example, the diagnosis of a suspicious lesion takes about a week or two after the biopsy but with the help of biochips it is possible to get the result within 10 to 15 minutes as the lesional cells can be scraped off with the help of brush and placed on the chips which are then analyzed with the help of an analyzer to get results within minutes [Ogle OE, Byles N.,2014].

Recombinant DNA technology

Recombinant DNA technology means cutting of DNA fragments of different genomes and joining them to make a single DNA having properties of the different genomes used. These methods are used to clone microbial DNA for periodontal disease diagnosis, prosthodontics and also has prognostic applications. Other uses include recombinant human insulin, recombinant human growth hormone, recombinant hepatitis B vaccine etc [Slavkin HC.,1989].

Recombinant DNA technology Transcriptome analysis, proteomics, metabolomics, nutrigenomics

In Transcriptome analysis [Wolf JB.,2013], mRNA and consequently gene expression is analyzed in a biological sample while proteomics deals with proteins in a biological sample [James P.,1997]. Metabolomics describes the quantitative analysis of all metabolites in cells or tissues [Bennett D.,2005]. Nutrigenomics unfolds the relationship between nutrition and human genome [Müller M, Kersten S.,2003].

CRISPR

CRISPR/Cas9 is a super selective and precise gene-editing tool that has applications in treating and curing genetic diseases and fighting cancer. CRISPR/Cas technology is a very easy means of developing disease models that accelerate the discovery and development of drug targets. It has immense scope and can be applied for the treatment of dental disorders.

CONCLUSION

Genetics is an ever-revolving sphere that constitutes an extremely important aspect of recent research and development and also can give a predictable outcome to a lot of dental issues and diseases at an early age where they can probably be corrected. Genetics and hereditary studies have proved to be crucial in understanding the origin of different oral health disorders. Various oral diseases such as dental caries, oral cancer, periodontal diseases, etc. have shown a stronger link for genetic predisposition which can be targeted in the focus of oral health. Understanding the relation between genetics and oral health enables patients to acknowledge patterns of dental disease occurring in families. Genetic studies have helped to identify different individuals in high-risk populations and helps in the implantation of various preventive measures. The winner of Nobel Prize 2020 Emmanuelle Charpentier and Jennifer A. Doudna came with the CRISPR/Cas9 method of genome editing which has been a boon for a biologists who use molecular scissors to probe the code of life in a fundamental science experiment. As new technologies are coming into the light, it has been easier to early diagnosis, thus preventing hazardous effects of the diseases so that they could be treated early. As genetics provides us with updated and accurate knowledge, more scientists and researchers should take a keen interest in this subject which can be encouraged by government funding. Continuing dental education while practicing dentistry is important, hence one must be updated about such new advancements in the health care industry.

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