Fulfilling the Promises: Contribution of Genomes for the Changing Dentistry
Ajay Bhamal, Sudhanshu Saxena, Manish Jain, Aishwarya Singh

Abstract

Genome contains all the biological information needed to build and maintain an organism. The mapping of human genes is a crucial step in the development of various aspects of health care, including dentistry. The human genome project, have recently opened immense opportunities for transformation of basic science discoveries to oral health care at the chair side through clinical research. This review aimed to summarize its implications in dentistry.

Key Words: Genome; Dentistry; Human Genome Project.

Received on: 10/09/2010   Accepted on: 14/11/2010

American social writer and philosopher Eric Hoffer wrote, “In times of drastic change, the learners inherit the future. The learned usually find themselves beautifully equipped to live in a world that no longer exists”.(1) The dentists today must understand human genetics and the rapidly changing methods for selectively and appropriately applying this new vast knowledge. Researchers today are faced with understanding the function, interaction (gene to gene and gene to environment), regulation of genetic material, and role of these factors in determining health and disease.(2) With advancement in genetic research namely the Human Genome Project, dentistry is expected to change dramatically in the future. (3)

We must understand that science has problem with individuality. Today we must rely on the tenet of “one disease, one treatment”. Diseases are now being defined as a genotype and/or phenotype that have the potential for adverse consequences. Even simple hereditary traits must be viewed as complex conditions. For oral diseases it gets necessary to understand genetic variability at an even greater level. Advancement in disease diagnosis and treatment is and will be determined by our growing ability to acquire new data and to efficiently analyze it.(2) Dentistry’s future will include the ability to customize patient treatment according to each patient’s genetic profile. The purpose of this review is to elucidate the genomic advantages of various common dental diseases, provide a framework for the likely future directions and challenges that will be faced by oral health professionals.

A genome is the complete set of genetic instructions carried within a single cell of an organism. It contains biological information needed to build and maintain organism. It is the genetic material in the chromosomes of a particular organism; its size is generally provided by the total number of base pairs. The biological information contained in a genome is encoded in its deoxyribonucleic acid (DNA) and is divided into discrete units called genes. It is the functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. Gene code for proteins that attach to the genome and switch on a series of reactions called gene expression. It is the process by the instructions encoded in DNA is converted into a unit of biological function in a cell.(4)

DNA is composed of chemical bases represented by four letters A, C, G and T. Determining the order of these bases is “sequencing”. That sequencing results in a person’s genome, which will tell health professionals the instructions for everything a patient’s cell does. All individuals share genome sequence that are 99.9% same. Only 0.1% is responsible for all genetic diversities. The use of genomic locations where a single base in the DNA sequence is altered may be informative for diagnosis of disease. This variation is known as single-nucleotide polymorphism (SNPs). Majority of SNPs have no deleterious effects. These are present through entire genome, and contribute to difference among individuals as tooth size and shape. While others effect risk for disease and associated with complex disease.(5) New technologies for genotyping and statistical analysis to separate disease related SNPs from normal genetic variation could make this approach useful for identifying genes associated with complex traits such as dental caries and periodontal disease.

Human genome project or the HGP is an international scientific research project. Its primary goal is to determine the sequence of chemical base pairs which make up DNA. Its aim is to map the nucleotides contained in a haploid reference human genome. With the objective of understanding the genetic makeup of the human species, it remains one of the largest single investigational projects in modern science.(6)

Since its inception in 1990, the HGP has yielded techniques and discoveries that will forever change the way we think about growth, development, disease and therapy. By June 2000, the project’s Public Consortium and Celera Genomics announced a working draft of the sequence of the human genome.

©INTERNATIONAL JOURNAL OF DENTAL CLINICS  VOLUME 3 ISSUE 3 JULY-SEPTEMBER 2011 70
95 percent of the genetic blue print for a human being is complete. It is 99.9 percent accurate. The project got completed in 2003, with further analysis still being published. Mapping "the human genome" involves sequencing multiple variations of each gene. The project did not study the entire DNA found in human cells. To sit down and read the amount of information generated by HGP would take 26 years of round the clock reading time.

The various genetic disorders related to dentistry can be grossly classified as simple or complex conditions. Simple conditions are those resulting from a single gene that has a major effect, whereas complex conditions are those resulting from a collection of altered genes interacting with environmental influences.

1. Simple hereditary oral health conditions

- **Congenitally missing teeth:** The prevalence of hypodontia varies between races and the specific tooth type. Based on various studies it can be said that congenitally missing primary teeth is less prevalent. The mandibular central incisor is the most commonly missing primary tooth. It is a genetically heterogeneous group of conditions. Different mutations in the multiple genes are together expressed to determine tooth type, location, and time of formation leading to its differences in prevalence of hypodontia.

- **Missing primary tooth:** It is a genetically heterogenous group of conditions. Different mutations in the multiple genes are together expressed to determine tooth type, location, and time of formation leading to its differences in prevalence of hypodontia.

- **Dentinogenesis imperfecta (DI) Type II:** The diagnosis is based on the absence of secondary dentin on teeth with usual anatomy. DI type II has been associated with mutations in the dentin phosphophosphate protein (DSPP) gene.

2. Complex hereditary oral health conditions

- **Dental caries:** Molecular markers have not been identified for specific hereditary factors that contribute to increased risk for or resistance to developing dental caries. Evidence suggests that heredity plays an important role.

- **Periodontal diseases:** Relationship for specific gene defect and periodontitis susceptibility can be illustrated by the association of severe periodontitis with a number of genetic diseases. Mutations of the cathepsin C gene are responsible for at least a portion of prepubertal periodontitis cases. Identification of gene mutations permits genetic testing, determination of a definitive diagnosis in these conditions. Genetic basis for forms of aggressive periodontitis is less well characterized. Susceptibility is inherited (simple genetic trait) how many genes are involved and is still unclear. Genes that modify clinical expression of disease form have been gamma receptor genotype, vitamin D receptor polymorphisms, and immunoglobulin allotypes.

- **Aggressive periodontitis:** It has complex etiology. The final disease phenotype is modified by multiple genetic and environmental factors. Chronic periodontitis - Heredity is a significant factor. It results from additive effect of multiple genes, interactive effects with other gene products, and through modulation by environmental factors. Naturally occurring genetic variants (genetic polymorphisms) are likely to impart genetic risk. These issues will gain more attention as it is generally realized that the ability to test for genetic polymorphisms exists before the meaning of test results is fully understood.
Head and neck cancer: Genetic model of head and neck squamous cell carcinoma (HNSCC) is complex. The risk of HNSCC is determined by effect of multiple different gene polymorphisms and environmental exposure of agents. (19) Understanding the spectrum of genetic susceptibility may help identify agents that increase risk for disease and individuals at greatest risk. (11) In the case of HNSCC, high levels of expression of certain genes, for example, the p65 subunit of the transcription factor kappa B (NF-kappaB) and IkappaB kinase, may contribute to malignancy. (20) Lack of the tumor suppressor gene PTEN may be an important prognostic indicator in squamous cell carcinoma of the tongue, while over expression of the hepatocyte growth factor MET oncogene is involved in invasive metastatic behavior of HNSCCs. (20, 21) High expression of epidermal growth factor receptor (EGFR) and the proliferating cell nuclear antigen (PCNA) have been correlated with short patient survival and are thus indicators of poor prognosis. Cyclin D1 (CCND1) is over expressed in a significant proportion of HNSCC and correlates with aggressiveness, early recurrence, and poor prognosis. (22) Antisense cyclin D1 may be useful, particularly in combination therapy, for instance with cispatin, in treatment of HNSCC. (19) Identification of genetic alterations may provide the basis for novel, highly specific, and sensitive diagnostic tests. (11)

An association between the presence of human papilloma virus (HPV) and the development of HNSCC has been established recently. (23) HPVs are small oncogenic viruses, which are implicated in epithelial carcinogenesis, and p53 is a tumor suppressor gene with a central role in prevention of genomic injury. (24) A critical molecular parameter supporting a causal role of HPV-16 in HNSCC is the expression of E6 and E7 oncoproteins coupled with inactivation of pRB and p53. (24) The tumors exhibited E6 gene expression and lacked p53 mutation or alternatively, they lacked E6 expression and carried p53 mutations. (24) Dentists will need to be familiar with a variety of genes, especially which are highly polymorphic in many populations and be able to understand and interpret data from a variety of studies to evaluate the claims suggesting association with HNSSC. (25)

Mortal and immortal squamous cell carcinomas also differ in the expression of p53 and Rb/E2F target genes, including the novel p53 target, DRAM. (25) Individuals with polymorphisms in the CYP1A1, GSTM1 genes, and zinc finger protein 217 have a genetically high risk of OSCC and tobacco-related cancers, suggesting that an individual difference in the susceptibility to chemical carcinogens is one of the most important considerations in the risk assessment of oral cancers. (26)

Wound healing process: The wound-healing process involves a complex interplay of cells, mediators, growth factors, and cytokines. (27) The list of events begins with clotting and recruitment of inflammatory cells and then proceeds to a highly proliferative state. RHuEPO gene is able to improve wound healing by stimulating granulation tissue formation neovascularization and dermal regeneration. This might be of particular relevance in the clinical situation of disturbed and delayed wound repair. (28) Smad3 and Smad2 (closely related homologue), are intracellular mediators of TGF-β function. They act as nuclear transcriptional activators and mediate intracellular signaling from TGF-βs 1, 2, 3, and activin, each of which has been implicated as an important factor in the cellular proliferation, differentiation, and migration pivotal to cutaneous wound healing. Disruption of the Smad3 pathway in vivo, coupled with exogenous TGF signaling through intact alternate pathways, may be of therapeutic benefit in accelerating all aspects of impaired wound healing. (29)

Dental Anomalies: The HGP has had a massive impact on the identification of the causes of inherited anomalies. Molecular genetic analysis makes the identification diagnosis and reporting of cases, and identification of the underlying genes. For dental anomalies, a large number of families with these conditions need to be identified and recruited. In a study conducted on 19 patients by Trevor et al. it was reported that patients with PAX9 mutations typically lack six or more molars, there was considerable intrafamilial variability in the identity of the teeth missing among affected members of the families within which various PAX9 mutations were reported to be segregating. The dental professional can facilitate this effort by collaborating with geneticists by referring families with these inherited anomalies for analysis. This will enable geneticists to identify the underlying genetic causes and further our knowledge of human dental development. It also will offer hope for new therapeutic regimens in the future so that we can move from a mode of diagnosis and treatment to one of prediction and prevention. (29)

There are certain changes required in the knowledge, attitude and skills of oral health professionals to care for patients. Following recommendations are made. Dental professionals should demonstrate foundational knowledge of fundamental genetic principles, including principles of genetic transmission, molecular biology of the human genome, principles of population genetics, working
knowledge of genetic terminology and applications of genetics to patient care.

Dental professionals should thus demonstrate the following skills: a) take a family history, recognize patterns of inheritance, and carry out basic genetic risk calculations; b) perform a head and neck examination with special attention to signs of major genetic disorders, c) consider genetic conditions as a contributor in a differential diagnosis and modify treatment to accommodate genetic conditions, d) recognize when to refer a patient for genetic screening, testing, and counseling, e) interpret results of genetic tests and explain them to patients and family members, f) explain and obtain informed consent for genetic testing, g) access and critically assess appropriate literature to determine the appropriateness of a referral, prescription, and treatment or of a genetic test, h) work collaboratively with other members of the genetics health care team, and emerge as dental geneticist.

Dental professionals should thus understand the following attitudes: a) the possibility that there is a genetic etiology for every patient, b) the potential for genetics to contribute to the development of new approaches to prevention, diagnosis, and treatment of disease, c) the potential for genetics to expand understanding of the basic pathophysiology of dental disease, e) the possibility of using a genetic approach to provide personalized health care, d) current limitations in the existing knowledge base, e) that the principles for use of genetic information in decision making are largely the same as for other areas of medicine, f) the rapidity of the advancing front of knowledge, g) that genetic information may have treatment implications not only for an individual patient, but also for an entire community, h) the need to reduce public fear and misinformation about geneticist i) the diversity in public understanding of genetic information and evaluation of information sources; and j) the need for continued learning and receptivity to advances in knowledge and changes in practice. (1, 5, 30)

There are many questions which remain unanswered when dealing with the human genomics. Some of these are: a) Societal concerns, who should have access to personal genetic information, and how will it be used? What about privacy and confidentiality of genetic information? b) Reproductive issues use of genetic information in reproductive decision making, and rights. How reliable and useful is fetal genetic testing? c) Clinical issues including the education of doctors and other health service providers. How will genetic tests be evaluated and regulated for accuracy, reliability, and utility? There are uncertainties associated with gene tests for susceptibilities and complex conditions linked to multiple genes and gene-environment interactions. These uncertainties leave us unanswered about whether testing should be performed when no treatment is available? Should parents have the right to have their minor children tested for adult-onset diseases? (2, 8, 18)

Modern science has surprised and dazzled our imagination. It has improved the oral health and quality of life for countless people and communities. We have learned that oral diseases have no anatomical or disciplinary borders. For the future of oral health care and research, we must take an advanced step towards solving complex oral diseases by the embracing best science, supporting new ventures and merging knowledge of people in other disciplines. Scientific research will continue to yield exciting technologies and effective treatments. Dental educators and clinicians will need to adapt to modernistic ways of providing care and applying new approaches for solving old problems. Doing so will ensure that dentistry is poised to inherit the future.

Present review has discussed the changes, challenges, and how oral health will soon be managed in era of genetic dentistry. Our genome “a genetic thumbprint” will provide health professionals including dental health professionals with the instructions for everything our cell does, from the time we began dividing into a zygote to the day we die. (30)

It has graced science like never before. The effect of the Human Genome Project on mankind will probably uncover in ways we can’t begin to imagine.

**Authors Affiliations:** 1. Dr. Ajay Bhambal, MDS, Professor and Head, 2. Dr. Sudhanshu Saxena, MDS, Senior Lecturer, Department of Public Health Dentistry People’s College of Dental Sciences and Research Centre, 3. Dr. Manish Jain, MDS, Senior Lecturer, Department of Public Health Dentistry, People’s Dental Academy, 4. Dr. Aishwarya Singh, BDS, Post Graduate Student, Department of Public Health Dentistry, People’s College of Dental Sciences and Research Centre, Bhopal, Madhya Pradesh, India.

**References**


Address for Correspondence
Dr. Ajay Bhammel, MDS, Professor and Head, Department of Public Health Dentistry, People’s College of Dental Sciences, Bhopal, Madhya Pradesh, India.
Ph: +91 98260 42852
Email: dr.sudhanshusaxena@gmail.com

Source of Support: Nil, Conflict of Interest: None Declared