Implications of genomics in oral health
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Abstract
In the last 10 years, there is a rapid improvement in the field of medicine. Scientific advances have made us understand the genetic basis of the diseases giving us the profound difference in the quality of life. Genetics is playing an important role in the diagnosis and management of diseases. Human genome project was the major step, which led to many discoveries in the field of genetics and genomics. This has opened us vast opportunities for translation of basic science research to oral health care. The present article reviews the role of genomics in oral health.

Keywords
Cancer, gene, genomics, human genome, oral diseases

Introduction
There is an increasing emphasis toward the evidence-based approach in the medical and dental health practice. The benefits of scientific advances have improved the quality of life of many individuals. Thousands of diseases have been identified in its initial stages and few are diagnosed even before the onset.\(^1\)

Interest in human genetics is not new, but our practical ability to apply the knowledge of genetics is relatively new and has fundamentally transformed the field of human genetics from an academic pursuit to an applied science.\(^2\)

Life is specified by genomes. The human genome is often referred as “Magic Wand,” a tool that identifies the underlying cause of the disease (one’s genes), determines what diseases are on the perspective, and summons up an array of effective tailored treatment to the individual patient.\(^3\)

Genome is the entire genetic makeup of the human cell nucleus or the sum total of all an individual organisms’ gene.\(^4\) Genome is defined as the master blue print for cellular structures and activities during the lifetime of each and every cell; the genome contains the complete set of instructions for the initiation, construction, operation, maintenance, and repair of all living organisms.\(^5\) Human genomics is the study of structure, function, and interactions of all genes in the human genome that promises to improve the diagnosis, management, and prevention of disease.

Many clinicians and the public have confusion between the two terminologies genetics and genomics; these two are not the same but two different entities. Genetics is the study of single gene whereas genomics is the study of the functions and interactions of all the genes in the genome.\(^6\)

Human Genome Project (HGP)
The HGP is an international scientific research project started in 1990 with a primary goal to determine the sequence of chemical base pairs which make up DNA and to identify genes in the human genome.\(^7\) This HGP is a large coordinated and multinational effort between public and private sectors to elucidate the genetic component and architecture of the human genome.\(^8\)

The human genome consists of two closely entwined threads of deoxyribonucleic acid or DNA which is organized as 23 distinct microscopic units called chromosomes. The DNA extends for the full length of the chromosome and according to the HGP, if unraveled would stretch out a distance of 5 feet but only be 50 trillionths of an inch in width.\(^9\) The full scope of human genetic information is immense. The human genome contains approximately 3 billion nucleotides, making up about 100,000 alleles, which in turn are present on 46 chromosomes. Transcription of these chromosomes releases the information necessary to synthesize some 6000 proteins. These proteins
make up the trillion cells giving rise to the nearly 4000 anatomical structures that constitute a single human being. The genomic information can be obtained from the nucleus of each human reproductive cell (sperm in testes and ova in ovaries) as well as the trillions of somatic cells (e.g. cartilage, bone, periodontal ligament, dental pulp, trigeminal ganglia, salivary glands, oral mucosa), genomic information is also encoded within genes located in the maternally inherited mitochondria termed the mitochondrial genome or mitDNA.

Heritable conditions or syndromes affecting any aspect of growth and development are due to the Mutation, the accidental alteration of the genome.

With the exception of trauma, almost all diseases and disorders have major genetic component. Human diseases and disorders may result from either single gene mutations or may result from complex and multiple gene-gene and gene-environment interactions.

About 99.9% of DNA sequences are exactly the same across the entire human population. Individuals are distinguished from one another by 0.1% difference in the nucleotide sequence of the human genome.

Genomic research is rapidly increasing our understanding of the genetic basis of normal and abnormal growth, development, and diseases. In the 21st century, the field of medicine has witnessed many new advances. With the completion of HGP in 2003 an enormous amount of new information has been gained about the sequencing of human DNA and the human genome. This HGP was a major step, which led to the ladder of scientific discoveries and has been beneficial to human genetics and genomics.

The achievements of genomics have inspired numerous omics disciplines such as proteomics, transcriptomics, metabolomics, epigenomics, glycomics, and pharmacogenomics facilitating us to understand the pathogenesis of disease leading to identification of new diagnostic markers and therapeutic targets.

Clinical Implications of Genomics

The treatment of oral, dental, and craniofacial diseases has drastically changed because of these new genomic advances, which are leading the researchers and clinicians to understand the oral biology. Genomic and proteomic advances combined with the power of superfast computers are helping us in understanding of oral, dental and craniofacial diseases. More precise and faster diagnostic tests, new drugs and biologics, practice-based research, and culturally sensitive interventions are providing novel avenues to improve oral health.

In recent times, genomics and related technologies will be incorporated into all aspects of health care including dentistry. The advances in genomics have led to a drastic paradigm shift in the field of oral medicine which may include clarity of disease etiopathogenesis, presymptomatic testing, and development of more robust disease nosology, diagnosis, prevention, and effective management. Genome-wide association studies (GWAS) also reveals the complete picture of the genome rather than smaller sections thereby allowing us to understand the cellular pathways and mechanisms of the disease process completely.

Genomic information can be applied at many important points during the disease progression starting from a healthy state to disease state. By assessing the DNA at healthy state, the disease susceptibility and risk can be quantified. Hence, there is a paradigm shift in the health planning strategy from disease treatment to disease prevention. An increasing emphasis is being placed upon developing an evidence base approach to clinical care and treatment.

The study of genomics has its greatest contribution to health by revealing mechanisms of common complex diseases such as hypertension, diabetes, and asthma. Some of the diseases where the genomics has unraveled the etiopathogenesis are breast cancer, colorectal cancer, human immunodeficiency virus infection, tuberculosis, Parkinson’s disease and Alzheimer’s disease.

Various diseases are caused by mutations; the most common mutation is the loss of function. MODY1, MODY2, and MODY3 increase the risk of diabetes. Parkinson’s disease is caused by the mutation of a synuclein gene.

Cancer is one field that has benefited by this genomic studies. Cancer is a heterogeneous group of diseases despite sharing the common aberrant physical alteration where it has got a diverse constellation of causes, pathogenesis, metastatic potential, and therapeutic response. Cancer is caused and driven by a sequential accumulation of genomic changes in cancer relevant genes. The interplay between genetic composition and environmental factors contribute to an individual’s predisposition to cancer even before the malignant transformation. Knowledge of this interplay will help in preventing the onset and progression of the disease by modifying the behavior and lifestyle of the patient.

The genomic revolution has laid a foundation for driving genetic signatures for prediagnostic genetic screening, tumor classification, and evaluation of patient prognosis determining the recurrence risk and therapeutic response and prognosis.

The genomic information can be obtained through genetic screening with a family history of oncogenic gene mutation such as in adenomatous polyposis coli, BRCA1 and BRCA2 gene (breast cancer). Genetic testing has also been used to identify patients with higher risk of developing colon cancer (mutation in the DNA, mismatch repair genes, MLH1 and MSH2) and multiple endocrine neoplasia type 2 (RET gene mutation).

The molecular analysis at the protein, DNA, RNA or micro RNA levels can contribute in the subclassification of the tumor.

Oral Implications of Genomics

Head and neck squamous cell carcinoma (HNSCC)

HNSCC is a disease with complex gene alterations that either shut down or amplify regulatory signals. Research has confirmed that HNSCC tumors associated with human papillomavirus
infection have a genetic profile different from that of tumors in individuals with a history of tobacco use.[36]

SNP A/G870 in the CCND1 gene encoding for protein cyclin D1 is associated with increased oral squamous cell carcinoma (OSCC) susceptibility and overexpression of this CCND1 is an indicator of the aggressive nature, early recurrence and poor prognosis. Overexpression of this gene is also correlated to radiosensitivity and, therefore, is a useful predictor of the effectiveness of radiotherapy.[28,30] Overexpression of cell cycle signaling genes such as in Erb B complex also contribute to OSCC.

Lack of tumor suppressor gene PTEN is a prognostic indicator in squamous cell carcinoma of the tongue. The over expression of hepatocyte growth factor MET Oncogene indicates metastatic behavior. High expression of epithelial growth factor and proapoptotic cell nuclear antigen (PCNA) in head and neck cancer patients indicates short survival and poor prognosis.[31]

Genetic polymorphisms in glucosyltransferase 1A7 (UGT1A7) gene, glutathione S-transferase genes (GSTM1 and GSTT1), and cytochrome P450 1A1 (CYP1A1) gene increases the risk of HNSCC among tobacco users.[32]

Dental caries and periodontal disease

The most prevalent oral diseases worldwide include dental caries and periodontal disease which challenges the oral cavity.[33] Periodontal disease is one of the most common oral diseases characterized by inflammation and destruction of the periodontium. This disease results from complex gene/environment interaction. Multiple gene polymorphisms in a particular cluster of genes appear to confer genetic susceptibility to environment risk factors such as tobacco products, microbial infections, medical and immunological compromise, alcohol consumption, osteoporosis and variety of medications, sex and age.[34] The genetic basis for several syndromic forms of periodontitis has been identified. Papillon Lefevre syndrome, prepubertal periodontitis (some portion), Haim Munk syndrome are caused by the mutation of cathepsin gene. Chediak Higashi syndrome is caused by the mutation of CHS gene and Leukocyte adhesion deficiency Type I is caused by the mutation of β-2 integrin gene.[35] GWAS study on aggressive periodontitis has shown that the patients with aggressive periodontitis have SNPs on chromosome 9p21.3.

Dental caries is an infectious disease where there are numerous host resistance and risk factors that are genetically determined. Many studies have shown that 40-60% caries susceptibility is genetically determined. Dental caries is influenced by numerous genomic factors, a mutation in SNP of Amel X, a gene coding for a protein, which is crucial for normal enamel development is correlated with increased caries susceptibility. Decrease in the proline-rich protein levels increases the susceptibility of dental caries.[35]

Defect in KLK4 gene coding for a protein expressed during enamel maturation causes a decrease in the hardness of enamel thereby increases the susceptibility of an individual to caries. Identification of specific gene changes and interaction aids the dentist in identifying the caries risk individuals so that more frequent oral hygienic maintenance and aggressive treatment plan can be established.[36]

Microbial genomics and oral infection

The oral microbial ecosystem is essential in maintaining both the oral and general health of the body. The microbiome of an individual is contributed by his genetic makeup, which would prevent the existence and action of certain beneficial pathogenic species. The genetic composition along with other factors such as poor oral hygiene, immunological disorders may shift the ecological cycle in the oral microbiome for disease activation and progression as in case of dental caries, periodontal disease, and oral cancer. The newer omics like microbiomics and metagenomics helps in understanding the microbiology and pathogenesis of oral diseases.[37]

Pain and taste sensation

Genetic variation also plays an important role in the perception of pain especially chronic orofacial pain and temporomandibular joint disorders (TMDs). HTR2A and COMT genes are associated with alteration in autonomic function and pain perception in TMDs. The potential risk factors associated with stress response, psychological well-being, and inflammation are linked to NR3C1, CAMK4, CHRM2, IFRD1, and GRK5 genes. Taste sensation is mediated by TAS2R38 and TAS1R2 genes.[38]

The sequencing of whole human genome has become relatively inexpensive with the rapid advancement in the field of genomic technology, because of the rapid growth we need to face some challenges and have to answer some questions: [39,40]

- Whether there will be any discrimination among the people because of the individual genome information.
- How should this genomic information be interpreted and used?
- Who should have access to it?
- How can individuals be protected from its improper disclosure or use?
- How should dentists prepare for the clinical use of genomic technologies to oral health care?
- Reimbursement of patients cost.
- Protecting the confidentiality of the genomic information is also a concern.[27]

Conclusion

The rapid evolution of these genomic and omic technologies coupled with bioinformatics there is a paradigm shift in understanding the molecular signaling and pathway of the disease to a more evidence-based approach to clinical care and treatment, but the translation of the genomic and omic discoveries in clinical practice and into the public or population level health benefit have always been slow and difficult because of the cost, ethical, and discrimination issues. The pace of this genomic transformation is at an accelerating pace in medical
practice, but this not so in dental practice.[41] The dental schools and colleges has to incorporate this genetics and genomics in the curricula so that the genomic technologies become the fundamental part to refine our ability to predict future disease, classify it on molecular basis for better diagnostic and prognostic precision.

References
