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Genomics – An Overview

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Abstract
Every organism, including humans has a genome that contains all of the biological information needed to build and maintain a living example of that organism. Genetics is playing an increasing important role in the diagnosis and management of disease. As the use of genetics in medical diagnosis and treatment increases, health care workers will require an understanding of genetics and genomic medicine. Molecular dentistry, the human genome projects have recently opened vast opportunities for translation of basic science discoveries to oral health care. This improved appreciation of pathophysiology may be applied into avenues of clinical utility. As a result medical and dental science is a threshold of unparalleled progress as a result of the advent of genomics.

Key Words
Gene, Genome, Health, Heredity, DNA.

Introduction

Humans have known for millennia that heredity affects health.[1] Science makes a difference in our lives. Scientific discoveries change our perceptions, our ways of thinking and our attributes about today and tomorrow.[2]

Life is specified by genomes. Our genome encodes an enormous amount of information about our beings i.e. our looks, our size, how our bodies work, our health, our behaviors, how we are and so on. 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.[3]

Genetics and genomics are not just about rare disorders any more, and it is no longer confined to the genetic specialist; it increasingly affects every facet of health care including dental practice.[4]

Although medical genetics has been an important part of health care for many years, it has not been a common component of dental practices in most dental offices.[5],[6]

Changes in medical practice are occurring atan accelerating pace under the influence of the elucidationof genomes. Medical genetics, once a tool for diagnosing a handfulof relatively rare diseases inherited in a simple mendelianfashion, has now expanded into new territories: the prediction ofa healthy person's risks of even common diseases such as cancerand cardiovascular disease; the analysis of patterns of geneexpression as an adjunct to conventional diagnostic methods,such as histopathology; and the evaluation of multigenic diseasesand responses to environmental agents and drugs. Knowledge aboutthe genomes of microbes is expanding the opportunities for diagnosing,preventing, and treating infectious diseases, and it is likelythat such knowledge will soon contribute to defending our nationagainst bioterrorism. But the full potential of a DNA-basedtransformation of medicine will be realized only gradually,over the course of decades, as we try to understand the contentof genomes and, most important, the physiological consequencesof variations in their sequence.[7]

The pace of this transformation will be limited not only bythe pace of discovery, but also by the need to educate practicingphysicians, their coworkers, and their patients about the usesand shortcomings of genetic information. Unfortunately, mostmedical schools do not anticipate the changes that moleculargenetics would bring to modern medicine. As a result, the ranksof medical geneticists are sparse, and many physicians strugglewith the new biology. Furthermore, the nation's battalion ofgenetic counselors has never grown to the size that would beneeded in order to compensate for these deficiencies. As a result, doctors, nurses, and the public will have to do some work ontheir own to learn about the genes and genomes that will progressivelychange medical and dental practice.[7]

As research continues on the genomic influences on disease etiology and methods of genomic analysis become increasingly practical for use in the clinic, there will come a point when the utilization of genomic technologies in clinical oral health care becomes unavoidable. Genomic testing could allow risk based long term planning for more effective dental disease prevention, reduce the uncertainty in diagnosis and prognosis, and guide the selection of drugs or treatment protocols that minimize harmful side effects to ensure a more successful outcome for patients.[5],[6]

History

The field of genetics was initiated by the work of GregorMendel who in 1865 proposed the basic laws of heredity basedon the observations from breeding pea plants.

- In 1901, William Bateson, the biologist coined the word 'Genetics'.
- In 1944 Oswald Avery, Colin Mcleod and Maclyn McCarthy discovered that DNA, and not protein, was the hereditary material in most living organisms.
- In April 1953Francis Crick and James

Watson discover double helical nature of DNA. It was their work that heralded the field of the 'New Genetics' by determining that the DNA molecule must have a helical structure to enable the replication of DNA in cell division.

- In 1956, the number of chromosomes was determined by Jo HinTjio and Albert Levan.
- During the 1980s an increasing number of genes involved in human health, growth and development were located and their sequence of coded information was described.
- The further realization of the potential for diagnosis and prediction of genetic conditions began with the initiation of the Human Genome Project (HGP) in 1990, established as an international research effort with the goal of producing a variety of biological maps of human chromosomes and determining the complete chemical sequence of human DNA: the substance that makes up genes.

The genome

All the genetic materialin the cells of a particular living organism is referred to as its genome. The human genome thus describes all the genetic material found in a human cell.[8]

It is the entire genetic makeup of the human cell nucleus or the sum total of all an individual organisms' gene.[10] The human genome is invoked as a sort of 'Magic Wand', a tool that identifies the underlying cause of illness (one's genes), determines what diseases are on the horizon, and summons up an array of effective therapies tailored to the individual patient.[11]

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.[12]

The haploid human genome consists of 3.2 billion nucleotide or base pairs (A, adenosine; T, thymidine; C, cytosine; and G, guanosine) with DNA that are distributed among twenty three distinct chromosomes (twenty two autosomes and one sex chromosome; either X or Y) within the nucleus of all 10 trillion cells that make up the human body.[13] Within the vast array of bases are encoded approximately 45,000 regulatory or structural genes and the necessary elements that control the regulation of genes throughout the lifespan of the organism.[14] In addition to the genomic information found within the nucleus of each human reproductive cell (sperm in testes and ova in ovaries) as well as the trillions of somatic cells (eg 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. Mutations in mitDNA are also associated with a number of human diseases and disorders.[15],[16]

Inaccurate beliefs about genetics persist, including the view that in the past it had no effect on the practice of medicine and that its influence today is pervasive. In fact for decades knowledge of genetics has had a large role in the health care of many. We have recently entered a transition period in which specific genetic knowledge is becoming critical to the delivery of effective health care for everyone.[1]

If genetics has been misunderstood, genomics is even more mysterious - what, exactly, is the difference? Genetics and genomics are two different entities. Genetics is the study of single genes and their effects whereas 'Genomics' a term coined only 20 years ago, is the study not just of single genes, but of the functions and interactions of all the genes in the genome. Genomics has a broader and more ambitious reach than doe's genetics[1] or in other words genetics is the study of inheritance and genomics is the study of genomes.[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 contained 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. Mutation, the accidental alteration of the genome, may result in heritable conditions or syndromes affecting any aspect of growth and development.[17]

With the exception of trauma, essentially all diseases and disorders have major genetic component. Human diseases and disorders may result from single gene mutations, but more commonly result from complex and multiple gene gene and gene environment interactions.[15]

Why gene identification?

It provides a basis for the complete and comprehensive understanding of the genetic basis of growth and development. This knowledge provides the frame work for the development of presymptomatic testing and intervention strategies that ameliorate undesirable outcomes.[5]

Gene identification is only the first step toward understanding of human disease at the most fundamental level.[18]

Purpose of gene testing[5]

- Provide information to improve clinical care
- Screening tool in presymptomatic individuals who are at risk because of family history or environmental exposure
- Screening for those whose risk of disease is unknown
- Understand the pervasive and neurological issues of TMJ and associated problems
- Confirm diagnosis and determine prognosis
- To help in the selection of most effective treatment option.

The Human Genome Project (HGP) is a large coordinated and multinational effort between public and private sectors to elucidate the genetic content and architecture of the human genome and in parallel, that of infectious microbes, animal models and plants with particular benefits for biopharmaceutical and nutritional advances.[21] Starting in October 1990 and continuing to advance even today, the Human Genome Project (HGP) has provided huge amounts of new (and often totally unexpected) knowledge, which has been highly beneficial to human genetics and genomics-as well as to pharmacogenetics and pharmacogenomics.[22]

Achievements of genomics and the knowledge of the sequence of human genome have inspired numerous

–omicsdisplines such as proteomics, glycomics and metabolic, mainly aiming to understand the signaling pathways that allow cells to divide, differentiate and die in a controlled manner.[23]

Proteomics is the study of the proteome, or the entire proteincomplement of a genome. The proteome consists of all proteinspresent in a cell or tissue at a given time and is far morecomplex than was originally proposed by the one-gene, onetranscript,one-protein hypothesis. Genomic and proteomic approaches provide complementaryinsights into many disease pathways.[24]

Individuals are distinguished from one another by a 0.1% difference in the nucleotide sequence of the human genome. In other words, all individuals share genome sequences that are 99%the same. Only 0.1% is responsible for all genetic diversity between individuals.These differences are often in the form of variations of a single base pair, called single nucleotide polymorphisms (SNPs). Individual SNPs often cause only a modest change in the resulting protein concentration or function. It is, therefore, the concurrent presence of a number of SNPs that determines susceptibility to disease development and progression, particularly for polygenic diseases. There is increasing evidence for a genetic basis to many complex diseases without monogenic transmission, including heterogeneous conditions such as heart failure, myocardial infarction and atherosclerosis.[25]

In complex genetic diseases, the genotype confers a susceptibility to disease, but the development of disease is dependent on interactions of genes with the environment and with other genes. The genotype-phenotypecorrelation is often not straightforward. The incorporation of transcriptomic and/or proteomic data will allow for amore complete picture that accounts for epigenetic and environmental influences to be elucidated.[26]

Pharmacogenomics

The greatest area of immediate clinical application of genomic technologies is pharmacotherapy, in which the ultimate goal is to maximize response and minimize toxicity. The 'one drug fits all' concept has shifted to the paradigm of 'the right drug for the right patient at the right dose and time'. Both drug efficacy and drug safety have the potential to be improved by genotype-based pharmacotherapy. Molecularly targeted therapies could address responsive subgroups more directly.[26],[27]

The management of chronic oral and craniofacial pain presents significant opportunities for pharmocogenomics.[27]

With pharmacogenomics we are approaching a new era of "personalized medicines" medicine. The concept of personalized medicine was anticipated bySir William Osler (1849-1919), a well-known Canadian physicianduring his time. He recognized that "variability is the lawof life, and as no two faces are the same, so no two bodies arealike, and no two individuals react alike and behave alike underthe abnormal conditions we know as disease". Personalizedmedicine has rapidly advanced the prediction of disease incidenceas well as the prevention of incorrect drug prescriptionbased on a person's clinical, genetic and environmental information that understands an individual patient at the genetic level and offers the optimum treatment.[28]

Most of the developmental malformations are genetically mutated. Hundreds of genetic mutations have been identified that results in facial developmental defects such as enamel (amelogenesis imperfect), dentin (dentinogenesis imperfect),bone (osteogenesis imperfect) and cartilage (chondrodysplasia).[19]

Many systemic chronic diseases and disorders such as diabetes, arthritis, osteoporosis, fibromyalgia, sjogrens syndrome and AIDS as well as therapies for systemic diseases can directly or indirectly compromise oral tissues.[15],[20]

Today we increasingly appreciate that head and neck cancers are relatively common. Oral and nasopharyngeal squamous cell carcinoma often are diagnosed at late stages of the disease progression, they usually have a poor prognosis (50%) for survival after 5 years. Multiple and sequential mutations are associated with oral, pharyngeal and tonsillar squamous cell carcinoma. Oncogenes, proto-oncogenes and tumor suppressor genes are implicated in oral cancer.[15]

By 2020, the impact of genetics on medicine will be even more widespread. The pharmacogenomics approach for predicting drug responsiveness will be standard practice for quite a number of disorders and drugs. New gene-based "designer drugs" will be introduced to the market for diabetes mellitus, hypertension, mental illness, and many other conditions. Improved diagnosis and treatment of cancer will likely be the most advanced of the clinical consequences of genetics, since a vast amount of molecular information already has been collected about the genetic basis of malignancy. By 2020, it is likely that every tumor will have a precise molecular fingerprint determined, cataloging the genes that have gone away, and therapy will be individually targeted to that fingerprint.[14]

Possible consequences of genomic research:

- Privacy and fairness in the use of genetic information, including thepotential for genetic discrimination in employment and insurance.
- The integration of new genetic technologies, such as genetic testing, intothe practice of clinical medicine.
- Ethical issues surrounding the design and conduct of genetic researchwith people, including the process of informed consent.
- The education of healthcare professionals, policy makers, students, andthe public about genetics and the complex issues that result from genomicresearch.[29],[30]

Genomic and proteomic approaches to medicine promise to revolutionize our understanding of disease initiation and progression. The dental profession especially the oral physician will be faced with determining how best to incorporate this knowledge and the resulting new technologies into our health care system. This improved appreciation of new technologies will refine our ability to predict future disease, classify illness on a molecular basis for better diagnostic and prognostic precision and design personalized therapies tailored to the individual.

In conclusion, this is a time of dramatic change in medicine. As we cross the

threshold of the new millennium, we simultaneously cross a threshold into an era where the human genome sequence is largely known. We must commit ourselves to exploring the application of these powerful tools to the alleviation of human suffering, a mandate that undergirds all of medicine.Many challenges remain to realizing the benefitsof personalized medicine, but thoughtful, well-designedinvestigations with currently available methodologies mayhelp us to overcome them.

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