Stephen T. Sonis *Editor*

Genomics, Personalized Medicine and Oral Disease

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Preface

Clinical applications of genomics and personalized medicine have transitioned from being on a theoretical wish list to becoming a transformational driver of medical practice. In the mere decade since the completion of the Human Genome Project, commercially available genetic tests now predict the behavior of certain breast cancers, help establish effective doses of Coumadin, determine the toxic potential of certain cancer drugs, or identify patients at risk for periodontitis. Many more clinical applications of genomics are in the pipeline which will have impact as diagnostics, risk predictors, or treatment determinants. Furthermore, gene-based therapy is maturing.

The mouth and its related structures represent a unique part of the human body. It is the only site in which two hard tissues (teeth and bone), different types of epithelium, and glandular tissue dynamically interact in an environment consisting of a myriad of microorganisms that is constantly bathed in a heterogeneous salivary fluid comprised of immunoglobulins, enzymes, and buffering agents. The opportunities for genes to influence the behavior of cells, saliva composition, and microorganisms are remarkable. Furthermore, the heterogeneity of its composition predisposes the mouth to a wide range of infectious, neoplastic and autoimmune diseases which range broadly in their frequency, severity and impact. And the mucosa and bone are frequent targets of toxicities of a range of therapeutic modalities. Genes govern the risk, course or response of almost every one of these conditions, whether their etiology is natural or iatrogenic.

The objective of this book is to catalyze the application of genomics to the diagnosis and treatment of oral diseases by comprehensively presenting focused discussions on the current state of knowledge. The first section of the book provides basic information about genetics, genomics, and personalized medicine and the informatical methods available to apply and organize genetic data so that it has clinical relevance. Recognizing the genetic robustness of the oral cavity, the introductory section also includes chapters on the oral microbiome and host genomics and response to infectious agents. The next two sections contain chapters which describe the genomics of specific oral diseases and conditions, including the genetic basis for mechanism and risk of treatment toxicities associated with cancer therapy and bisphosphonates. Four chapters focus on gene-based therapies and the

pharmacogenomics applied to oral disease. The book concludes with a provocative summary which describes a comprehensive vision of the melding of genomics to personalized medicine and the potential actionable outcomes that will likely affect clinical practice in the upcoming years.

Despite the biological complexities of many oral diseases, their heterogeneous etiology, and the opportunity for the genome to impact their risk, course and response to therapy, there is no comprehensive (or even incremental) discussion of the topic among the many fine texts on genomics and personalized medicine. It is my hope that this book will fill that void.

Stephen T. Sonis, DMD, DMSc

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Fundamentals of Genetics and Genomics

Stephen T. Sonis

Introduction

When we think about genetics, we typically think of patterns of inheritance that affect us and our environment. Will our kids have blue eyes or brown? Is there a risk of a particular disease in our family? Can I eat a gluten-dense pizza with impunity? Rarely do most of us give much thought to the biological processes that control the variables that impact phenotypes. But as more and more has been learned about biology, and especially human molecular biology, it has become clear that almost every physiologic function and risk of pathology, whether organic or behavioral is, at least in part, genetically controlled. Genetics studies the individual genes, while genomics is more dynamic in that it looks at the interaction between genes and genes and the environment.

Historically, the diagnosis and treatment of diseases has been based on the belief that if we effectively address the normal distribution of disease risk, diagnosis and response to treatment, we're effectively addressing the proper clinical problem. But is this true? Probably not. What if you developed a drug that was incredibly effective for a deadly disease, but only for those individuals who had a specific gene to metabolize the agent? And what if that gene was only present in 15 % of the population? If you designed a classic clinical trial in which you tested your drug against a placebo and only 15 % of the study population responded, the test might be deemed a failure.

Gregor Mendel, that famous Austrian Monk with the peas, published his Laws of Inheritance at around the time of the American Civil War. But it wasn't until 1902 that an English physician, Archibald Garrod, made a connection between genetic traits and disease risk when he noted familial patterns of an obscure condition called alkaptonuria. And while DNA was described in 1869, it wasn't until the early 1950's that its role in mediating heredity and its structure were noted. Since then

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major advances in cell and molecular biology, genetics and genomics have established, not only the biological importance of the genome in affecting disease risk, but also have provided major opportunities for the translation of genomic information into clinically meaningful and actionable information. Genes have now been associated with cancer and heart disease risk and also with how patients respond to certain drugs, both therapeutically and in terms of toxicity or adverse reactions.

Recognizing the clinical potential of genomics, in 1990 the Office of Health and Environmental Research of the U.S. Department of Energy set about establishing the Human Genome Project. As described in a monograph on the topic by Palladino [15], the HGP had eight objectives of which the first four were probably the most directly relevant to clinical genomics:

- Create genetic and physical maps of human chromosomes.
- Identify the entire set of genes in the DNA of human cells.
- Determine the nucleotide sequence of DNA base pairs that comprise the human genome.
- And analyze genetics variations among humans, including the identification of single nucleotide polymorphisms (SNPs).

The objective of this book is to take a look at the most current information around genetics as it relates to oral diseases and to understand how all of this sophisticated science can be used in a way that ultimately is translatable to patients.

The Fundamentals: Chromosomes, DNA and Genes (Figure 1)

The genetic epicenter of the cell is its nucleus. In humans (not all animals have the same number of chromosomes) the nucleus contains 23 pairs of chromosomes of which 22 pairs are similar looking and called autosomes. The remaining pair are the sex-determining X and Y chromosomes (Fig. 2). Chromosome numbering reflects size—one is the largest. If the number of chromosomes is abnormal because of a consequence of faulty division, the result is an anomaly, often reflected as a defect at birth. Probably the most common example is Down syndrome in which there are 3, rather than a pair of chromosome 21.

The most significant structural component of chromosomes is DNA (deoxyribonucleic acid). Each chromosome contains a coiled strand of DNA which is wound around an alkaline protein core of histones. The unit of DNA and histone forms a fiber which is termed chromatin. One complete copy of a chromosome pair is designated as the chromatid and is joined to the other copy by the centromere.

If there is one molecule that is ubiquitously associated with genetics, it would have to be DNA. The story behind the discovery of DNA, the realization of its role in genetics and its structure and mechanism of action is among one of the most compelling in the history of science and was comprehensively reviewed by Petter Portin [16].

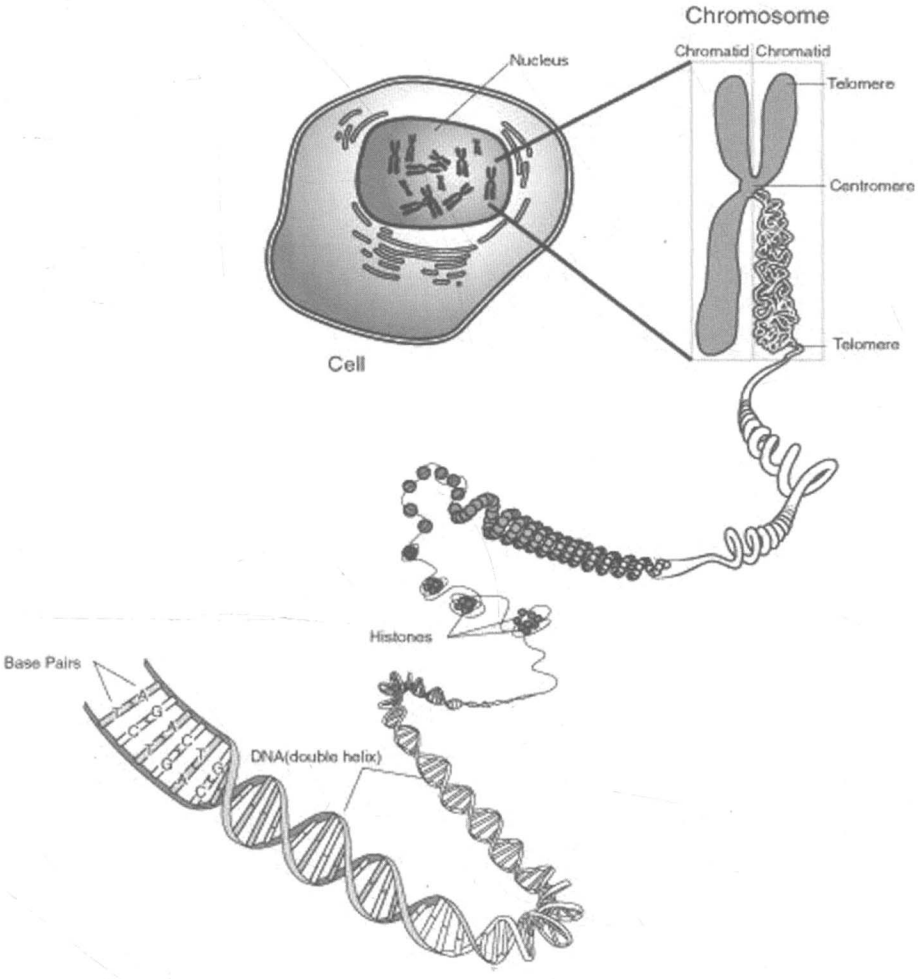

Fig. 1 The basics. The nucleus contains 23 pairs of chromosomes which contain strands of DNA wrapped around a histone core. DNA is composed of opposing strands (a double helix) joined together by base pairs (adenine [A], guanine [G], cytosine [C], and thymine [T]. Base pairs always join in a specific way: A-T or G-C. Each base is joined to a sugar phosphate backbone which together (base, deoxyribose sugar, and a phosphate group) define a nucleotide. Courtesy: National Human Genome Research Institute

Although it could be said that the DNA story culminated with the Nobel Prize winning description of its structure by Watson and Crick in 1953 [21], at least half a dozen other events were critical to its understanding [17]. At about the same time that Mendel was working out his Laws of Inheritance, Freidrich Miescher (1869) identified DNA from the nuclei of human white blood cells obtained from pus which he called nuclein. Shortly thereafter, the botanist Edward Zacharias made the link between nucleic acids and chromosomes. A critical discovery which localized genes in nuclear chromosomes was made in the early 1900's by Boveri and Sutton.

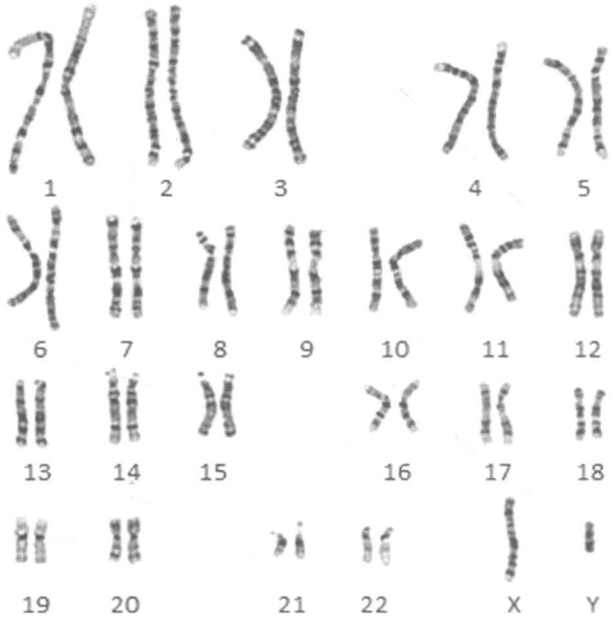

Fig. 2 Karyotype of human chromosomes. Chromosomes contain genes within their DNA. The size of chromosomes varies—1 being the largest and 22 the smallest. Likewise, the number of genes on each chromosome also varies. Genes occur along parts of the DNA and there's plenty of DNA that is not associated with protein-coding genes. In the past the non-gene DNA was given the misleading title of "junk DNA"

The completion of the chain linking chromosomes, genes and DNA occurred while World War II was raging. In 1944, in studies using pneumococcus, Oswald Avery, Collin MacLeod and Maclyn McCarty working at the Rockefeller Institute concluded that DNA was the carrier code and responsible for hereditary characteristics. Shortly thereafter, Edwin Chargaff successfully established the proportions of DNA's nucleic acids (Chargaff's rule) in which the amounts of adenine and thymine were equal to each other as was the case with guanine and cytosine.

In 1953, Watson and Crick described the double-helical structure of DNA to which we refer today (Fig. 3). Two strands DNA are composed of three fundamental building blocks: a sugar-phosphate "backbone" for each strand (the sugar is deoxyribose) bound together by reciprocal bases of adenine and thymine or guanine and cytosine. The combination of phosphate-sugar and a base is termed a nucleotide. The units of either A-T or G-C are called base pairs.

Genes are strung out long the length of each chromosome. Each gene is comprised of varying numbers of base pairs (see Table 1), but doing the math it's clear that there are many more base pairs than there are genes. In addition, the functional part of a gene, that is that part of a gene that is actually responsible for coding proteins represents under 10% of the base pairs in the gene. The non-coding portion of DNA was referred to a "junk DNA", but recent studies have demonstrated that junk DNA plays a role in a variety of functions having clinical significance including disease and toxicity risk [3].

Gregor Mendel

Friedrich Miescher

Oswald Avery

Francis Crick and James Watson. Copyright Science Public Library.

Fig. 3 Putting faces with names. Gregor Mendel, an Augustinian friar, is considered to be the father of modern genetics for his studies on inheritance at about the time of the American Civil War. Soon after (1869) Friedrich Miescher isolated nucleic acid from the nuclei of leukocytes. It wasn't until 1944 that Oswald Avery noted that genes were composed on DNA. In a little over 9 years, Watson and Crick, aided by information from the chemist and crystallographer, Rosalind Franklin, described the structure of DNA

Mutations and Variations in Genes

From a clinical standpoint, mutations and variations in genes play a big role in determining patients' risk of disease, how they respond to treatment or whether they're at high risk for certain drug toxicities or reactions. The fact that genes can

Table 1 The numbers game [15]

Number of human chromosomes	22 pairs + 2 sex chromosomes
Number of human genes	About 25, 000
Number of base pairs in human cells	About 3 billion
Number of base pairs in a gene (average)	3000 (largest 2,400,000)
Number of single nucleotide polymorphisms (human)	About 10 million
Frequency of SNPs	Once in every 300 base pairs
Number of genes on each chromosome	Varies by chromosome

change over time (maybe an extended period or acutely) in response to the environment in its broadest sense ultimately can influence phenotype. Changes in genes are called mutations and, by definition, a mutation is an alteration of the nucleotide sequence of a gene. Importantly, not all mutations result in disease, risk of disease or bad outcomes. The clinical importance of mutations varies. While all mutations are the consequence of nucleotide changes in sequence of a gene, some are subtle so show up infrequently and others are dramatic. Mutations which impact protein production in some way probably have the most impact clinically.

Mutations can be classified in a number of ways. Some describe their impact, while others are more descriptive relative to DNA morphology. Not all mutations are the same and not all have the same consequences. One way of classifying mutations is based on their impact on protein function. In this scheme, there are four possibilities:

1. Among the most common mutations are those associated with loss of function. Patients who have genetically-controlled enzymatic failures are representative of this category. One example are patients who don't have the enzyme to metabolize cancer chemotherapy drugs like methotrexate or 5-fluorouracil [6, 5, 18]. These type of drugs are toxic in their own right. You can imagine what happens when they're administered and continue to build up and stick around because the patient can't eliminate them. The levels of toxicity that affect patients in this category, like oral mucositis is horrific.
   Another example of diseases associated with this type of mutation are the diseases associated with inborn errors in metabolism [4]. A classic example of such a condition is phenylketonuria (PKU). Kids with PKU lack the enzyme phenylalanine hydroxylase which is critical to breaking down phenylalanine, a key component of proteins. As a result, if a child eats foods containing protein, phenylalanine accumulates and results in a range of symptoms and problems.
2. The opposite type of mutation may also occur in which there is a gain in function. As noted earlier, patients with Down syndrome have 3, not 2, #21 chromosomes.
3. Novel property mutations are those in which a specific gene change results in a clinical condition. Sickle cell anemia presents a good example [7, 13]. Sickle cell anemia is the most common blood disease in the United States and it affects thousands of patients worldwide. Due to a mutation of a single nucleotide (see SNPs below) the production of normal hemoglobin production does not occur and patients with the condition produce hemoglobin S.
4. Inappropriate gene expression characterized many of the genes identified with malignancies.