Cardiovascular Genetics and Genomics

Principles and Clinical Practice

Dhavendra Kumar
Perry Elliott
Editors

Springer

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Dedicated to Sir William Harvey (1578–1657)
Discovered circulation of the blood through arteries, veins and the heart

Foreword

The pace of advance in genetics and genomics in the last decade, underpinned by increasingly powerful technologies to interrogate the genome, has been such that it has moved from just being a field of elegant discovery science explaining disease mechanisms to one of progressively greater clinical utility and applicability. It is no longer beyond the realm of possibility, as is currently being explored in the UK 100,000 Genome Project, that all of us may one day have our genomes sequenced as a matter of course to aid with clinical diagnosis and management. All these new developments are laying the foundation for genomic and precision medicine, a concept that is being increasingly promoted globally as one way to tackle the increasing costs of healthcare.

In this context it is no longer possible for clinicians to ignore the potential and value of genetics and genomics to their practice as well as understand the limitations. Genetics affects many aspects of cardiovascular diseases—from causing Mendelian disorders such as hypertrophic cardiomyopathy and Marfan syndrome to contributing to the development of common and multifactorial disorders such as coronary artery disease and hypertension.

Building on their first edition published in 2010, in this revised and practically re-written new textbook on "Cardiovascular Genetics and Genomics-Principles and Clinical Practice", Dhavendra Kumar and Perry Elliott have assembled an outstanding group of contributors to cover the full spectrum of cardiovascular disorders where genetics makes a contribution. The book not only updates the state of the art with respect to conventional cardiovascular genetic disorders but also explores less traditional aspects such as the contribution of genetic analysis to the investigation of sudden cardiac death syndrome. Throughout the focus is on providing factual and easy to follow information that can help to inform clinical practice. The first section provides helpful background information about the nomenclature and approaches in genetics and genomics while other chapters deal with important issues such as principles and practice of genetic counselling and the value of the multi-disciplinary team approach.

With almost daily reporting of new associations of genetic variants with diseases, a book of this type cannot serve as a comprehensive compendium of such associations. What it does provide is a framework for clinicians to understand the genetic basis of cardiovascular diseases and when and how to incorporate genetic

information into their clinical practice. It is also an excellent primer for those in training and those allied health professionals interested in genetic/genomic medicine.

I am confident that you will find the book of great value as you dip in and out of it!

Nilesh J. Samani
BHF Professor of Cardiology, University of Leicester,
The Medical Director, British Heart Foundation
London, UK

Preface

> Where is the Life we have lost in living? Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?—T. S. Eliot

In 2010, we compiled, authored, and edited the first textbook on clinical cardiovascular genetics—"*Principles and Practice of Clinical Cardiovascular Genetics"* (ISBN-10:0195368959 & ISBN-13:978-0195368956, Oxford University Press, NY, USA). It was an ambitious project given many unproven hypotheses, incomplete evidence, loose fragmented scientific concepts, and controversial clinical applications. Nevertheless, the project was completed with the help of several experts from clinical cardiology, cardiovascular surgery, clinical genetics, genetic counseling, basic genetics and genomics, laboratory genetics, and many other health professionals. Fortunately, we were encouraged to receive largely welcome and positive feedback from medical, scientific, and allied health professionals.

Following the launch of the book, we were humbled to receive instructions and commission from Oxford University Press to produce a user-friendly specialist handbook for ready use and quick reference on factual clinically relevant information on inherited cardiovascular conditions. This Oxford specialist handbook further strengthened the new field of clinical cardiovascular genetics within the large field of clinical cardiovascular medicine. Subsequent years examined the purpose and applications of this new specialist field within the broad landscape of clinical medicine and clinical genetics.

The next five years witnessed exponential growth and enhanced genetic and genomic scientific applications and translations in many medical and health fields. The practice of cardiovascular medicine and surgery incorporates genetics and genomics that led to significant changes to the training curriculum and aspects of continued professional development necessary for enhancing the scientific basis of the clinical cardiology practice. This development is in line with other medical specialist fields, such as clinical oncology, medical ophthalmology, clinical rheumatology, clinical neurology, and many more. Genomic medicine is now a reality, not just a hypothetical scenario. This is now the agreed basis for personalized, precision and preventive medicine.

With the rapidly increasing quantitative and qualitative growth in the genetic and genomic knowledge base and evidence in cardiovascular medicine, the peer demands and expectations grew and persuaded us to revise and produce a new

textbook. We debated and consulted many colleagues, trainees, and students on the likely format and title of the new book. It became clear that despite controversies surrounding the use of genetics and genomics, the new title would need to reflect these two intricately connected scientific fields. Further, we agreed to give the book much needed clinical focus moving away from the conventional scientific introduction. We are convinced that the title and the format of the new textbook on inherited and genetic aspects of cardiovascular medicine and surgery clearly reflect the genetic and genomic basis of the clinical practice.

The book includes 31 chapters written and contributed by leading experts in specific scientific fields and recognizable inherited cardiovascular conditions. The first five chapters cover the basic aspects including one chapter on cardiovascular pharmacogenomics and pharmacogenetics. The format is largely clinically focused with examples reflecting patient and family stories managed by evidence-based clinical and genetics input. Wherever possible and applicable, the key practice points are highlighted in the box style. Concluding 3 chapters focus on interventional cardiology, the multidisciplinary care and public/population health. Readers will have the benefit of the detailed and carefully compiled glossary with most commonly used terms and phrases in the emerging new field of clinical cardiovascular genetics and genomics. Each section of the book is thoroughly indexed in the end to assist the reader fast and efficient access to any term or description to the respective page and paragraph.

Finally, this book could not have been written and presented in the current format without sincere and painstaking efforts of all contributors and the publishing team. We remain greatly indebted for their kindness and generosity. We humbly submit this book to all students, trainees, and practitioners in clinical cardiovascular medicine and surgery, clinical genetics, genetic counseling, cardiac specialist nursing, public health practitioners and professionals, and other health professionals. The feedback and reflections on the book would be welcome in whatever quantitative or qualitative manner. We remain aware of possible errors and omissions and collectively take full responsibility.

Cardiff, UK
London, UK
September 2017

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Introduction to Genes, Genome and Inheritance

1

Dhavendra Kumar

Abstract

The introductory chapter introduces genes, genome, genetics and genomics in simplified manner that, irrespective of any specialty, any clinician or healthcare professional should know. In addition to core basic information on nucleic acids, structure of the gene and organisation of the whole genome, the text includes clinical examples relevant to cardiovascular medicine and surgery. Selected examples might be of interest to medical and healthcare professionals predominantly engaged with cardiovascular conditions. Emphasis is given on developing reasonable grasp of genetic or genomic factors, heritable, incidental or somatic, that is either etiologically relevant or capable of influencing the natural course of any cardiovascular disease, acting alone or in combination with environmental (infection and toxins etc.) or life style factors (nutrition and occupation etc.). The text is supported with generous illustrations, tables and boxes with key learning points.

Keywords

Nucleic acids • DNA • RNA • Gene • Genome • Genomic variation • Single nucleotide polymorphism • Copy number variation • Mendelian inheritance Complex disease • Genomic medicine

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1.1 Introduction

Most medical practitioners and specialist physicians are oblivious of basic biological facts that govern the whole body and organ specific structure and function. In this context, understanding genes, genome, genetics and other intricately related facts are most fundamental to structure and function of any form of life. Higher mammals, including humans, have evolved over several thousands of years through repetitive cycles of transmission of genetic traits under enormous environmental pressures. Thus it is not surprising to find many unexplained and complex elements with the human genetic make up or genome. The human biology is perhaps one of the most complex and intriguing life sciences. Major organs and arbitrarily set out body systems have specifically assigned parts of the genome as the common denominator of structure and life long functioning. Nevertheless, system wide approach is relevant to medicine. In this context, understanding the role of genes and related elements of the human genome are pertinent to any medical practitioner, whether general or system specialist, such as the cardiovascular physician.

The present chapter introduces genes, genome, genetics and genomics in simplified manner that any clinician or healthcare professional should know. The broad spectrum of genetics and genomics includes many aspects of the genome (Fig. 1.1). Cardiovascular genetics and genomics are broadly similar to any other body system. Selected examples might be of interest to medical and healthcare professionals predominantly engaged with cardiovascular conditions. Emphasis is given on developing reasonable grasp of genetic or genomic factors, heritable, incidental or somatic, that is either etiologically relevant or capable of influencing the natural course of

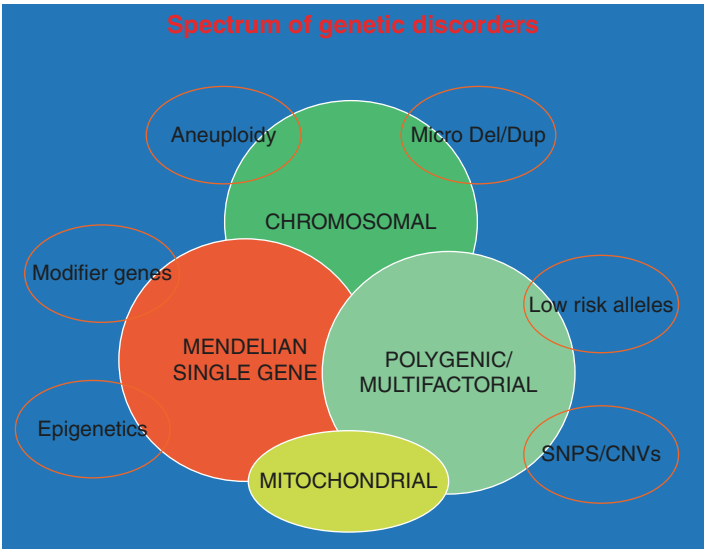


Fig. 1.1 Spectrum of genetic and genomic disorders; a genetic or inherited cardiovascular condition may be caused by one of these mechanisms

any cardiovascular disease, acting alone or in combination with environmental (infection and toxins etc.) or life style factors (nutrition and occupation etc.). The text is supported with generous illustrations, tables and boxes with key learning points. An interested reader or student might like to choose any book or resource listed under 'Further reading'.

1.2 Basic Facts: Cell Biology, Nucleic Acids, Gene, Genome

1.2.1 Human Genome: Structure and Functional Organization

Living organisms have two types of cells- nucleated, called *eukaryotes* and non-nucleated, called *prokaryotes*. Bacteria are essentially prokaryotes and all other multi-cellular organisms are basically eukaryotes. The total genetic constitution in either cell is called genome. In eukaryotes, it is contained within the nucleus and hence referred to as *nuclear genome*. However, the cytoplasm of a eukaryote cell also contains another genome within the energy rich intracellular organelle, mitochondria, referred to as the *mitochondrial genome*. Morbid changes in both genomes are associated with a number of human disorders. The cardiovascular system, by virtue of its diversity, complexity and high energy turnover, has many disorders caused by pathogenic changes in either the nuclear DNA (nDNA) or the mitochondrial DNA (mtDNA).

Genetic information is transferred from one generation to the next by small sections of the nucleic acid, deoxyribonucleic acid (DNA), which is tightly packaged into subcellular structures called *chromosomes.* Prokaryotes usually have a single circular chromosome, while most eukaryotes have more than two, and in some cases up to several hundred. In humans, there are 46 chromosomes arranged in 23 pairs, with one of each pair inherited from each parent (Fig. 1.2a, b). Twenty-two pairs are called *autosomes,* and one pair is called *sex chromosomes*, designated as X and Y; females have two X chromosomes (46, XX) and males have an X and a Y (46, XY).

A chromosome consists of a tightly coiled length of DNA and the proteins (e.g., chromatins) that help define its structure and level of activity. DNA consists of two long strands of nucleotide bases wrapped round each other along a central spine made up of phosphate and sugar (Fig. 1.3). There are four bases: adenine (A), guanine (G) cytosine (C), and thymine (T). Pairing of these bases follows strict rules: **A** always pairs with **T**, and **C** with **G**. Two strands are, therefore, complementary to each other.

Genes are made up of specific lengths of DNA that encode the information to make a protein, or ribonucleic acid (RNA) product. RNA differs from DNA in that the base thymine (T) is replaced by uracil (U), and the sugar is ribose. It acts as a template to take the coded information across to ribosomes, a major intracellular organelle, for final assembly of amino acids into the protein peptide chain (Fig. 1.3). The bases are arranged in sets of three, referred to as *codons.* Each codon "codes" for a specific amino acid; hence the term *genetic code.* Codons are located in *exons,* which contain the coding sequences. A gene may consist of several such coding DNA segments. Exons are separated from each other by non-coding sequences of

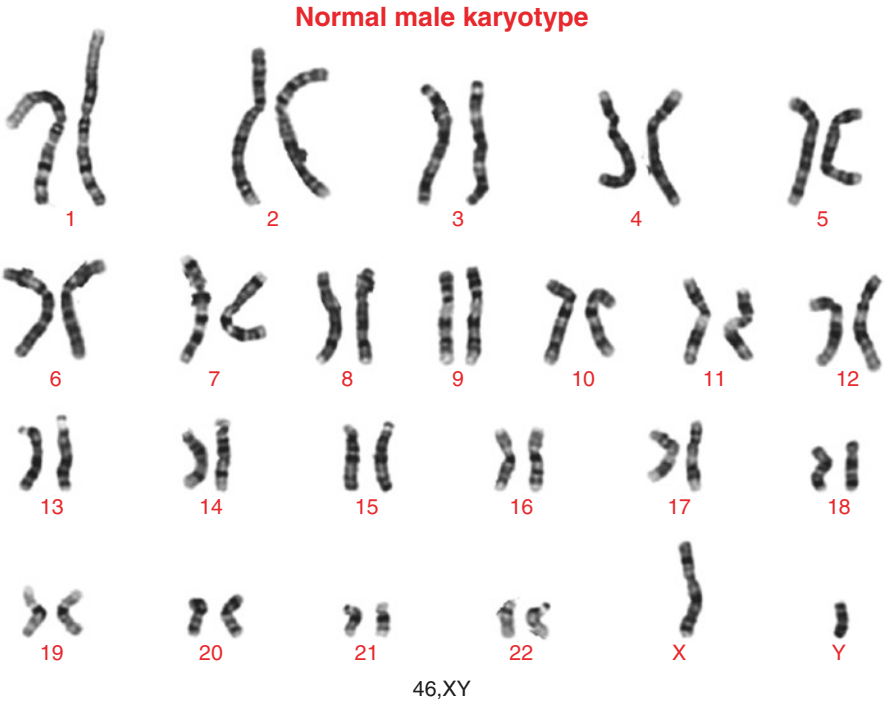


Fig. 1.2 A normal male karyotype- note small Y chromosome in the last chromosome pair

DNA, called *introns.* Although they are not yet known to be associated with any specific function, it is likely that some of these introns might be of evolutionary significance, or associated with other fundamental biological functions. During the transcription of DNA, the introns are spliced out, and the exons then attach to messenger RNA (mRNA) to start the process of protein synthesis (Fig. 1.4).

Proteins are one of the major constituents of the body's chemistry. These are remarkably variable in their structure, ranging from tough collagen that forms connective tissue and bone, through the fluid hemoglobin that transports oxygen, to thousands of enzymes, hormones, and other biological effectors and their receptors that are essential for the structures and functions of the body. Each protein is made up of one or more peptide chains consisting of series of amino acids, only of which 20 occur in living organisms. The different structures and functions of proteins depend on the order of amino acids as determined by the genetic code (Table 1.1: List of amino acids and Table 1.2: The Genetic code).

DNA has the remarkable property of self-replication. The two strands of a DNA molecule separate as chromosomes divide during cell division. There are two types of cell division; *mitosis* in all body cells, and *meiosis,* which is specifically confined to the gonads in making sperm and eggs. During mitosis, no reduction of the number of chromosomes takes place (*diploid*, or 2n), while meiosis results in half the number of chromosomes (*haploid*, or 1n). The new pairs of DNA are identical to

those from which they were synthesized. However, sometimes mistakes or mutations occur. These usually result from substitution of a different base, or are due to extensive structural changes to genes. In other words, any "spelling mistake" in the letters A-T or C-G could result in either complete absence of the coded information (*nonsense mutation*) or a different or alternative message (*missense mutation*). However, not all mutations or spelling mistakes have an adverse effect (*neutral mutations*). Conversely, some changes in the genes might result in a favorable property; for example, resistance to disease or other environmental hazard. This is the basis for the gradual changes in species over millions of years of evolution. On the other hand, mutations may result in defective gene functions, leading to a disease, or susceptibility to a disease, due to qualitative or quantitative changes in the gene product, the peptide chain. However, these changes may also result from epigenetic mechanisms, abnormal RNA molecules, and post-translational modifications (see Glossary).

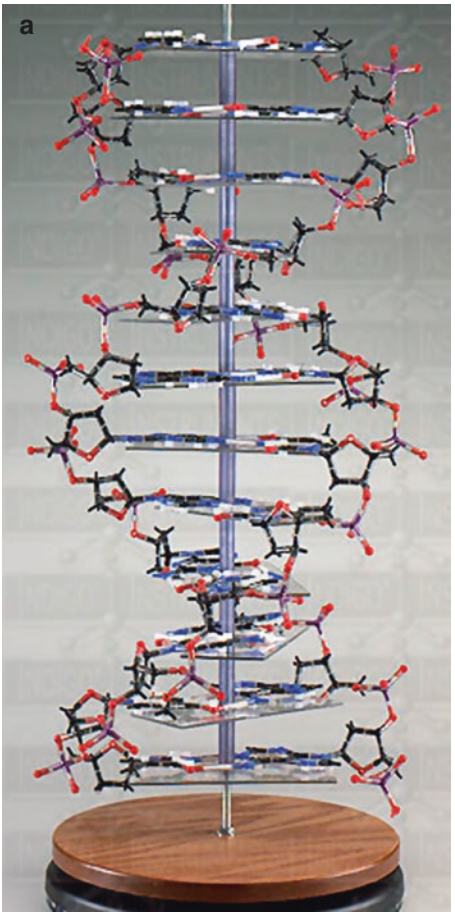
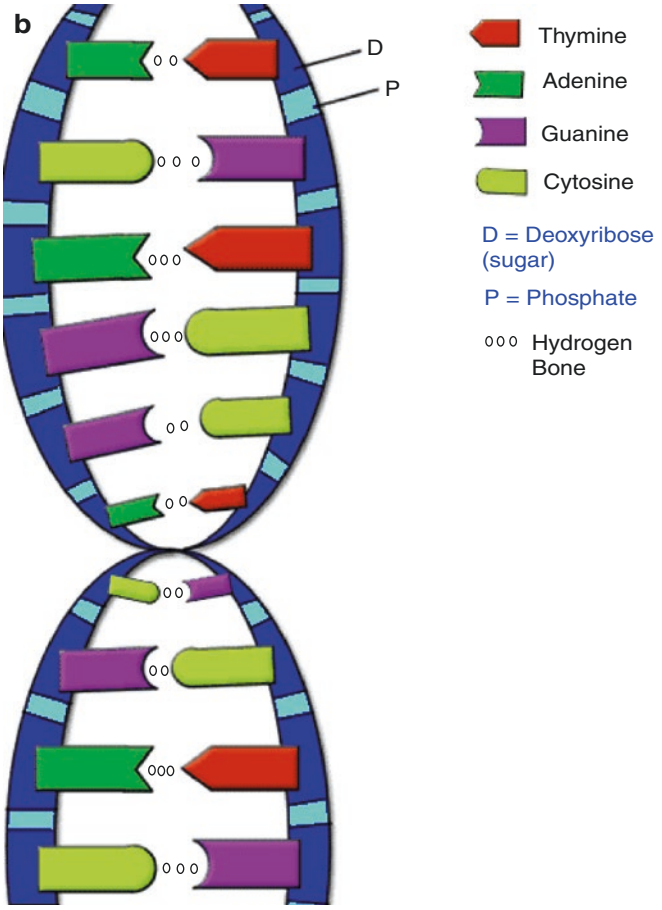


Fig. 1.3 The Watson-Crick double helix model of the nucleic acid (DNA) molecule. (**a**) Replica of the original model. (**b**) Graphic display of position of 4 bases (nucleotides), deoxyribose sugar, phosphate molecule back bone and the hydrogen bonds



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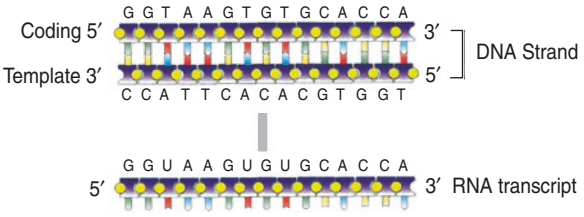

Fig. 1.4 Relationship of the double stranded DNA molecule (coding strand and the template) and the single stranded RNA molecule showing the transcript for translation

In brief, the human genome includes all coding and non-coding sections of DNA, interspersed sections of DNA of possible evolutionary or epigenomic significance, variable length of repetitive DNA sequences (polymorphisms), sections of RNA involved in transcription and translation, other RNA sequences involved in supporting biological functions, the compact mitochondrial genome (see next section) and ribosomal RNA. Apart from reproduction, genes, gene-sequence variation, genomic variation, and epigenetic factors are important in growth, development, aging, and

Table 1.1 List of amino acids with abbreviations

Alanine	A	Ala
Arginine	R	Arg
Asparagine	N	Asn
Aspartic acid	D	Asp
Cysteine	C	Cys
Glutamine	Q	GLN
Glutamic acid	E	Glu
Glycine	G	Gly
Histidine	J	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Selenocysteine	U	Sec
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val

Table 1.2 The genetic code

BASE 1	BASE 2	BASE 3
U	Phe Ser Tyr Cys	U
U	Phe Ser Tyr Cys	C
U	Leu Ser STOP STOP[a]	A
U	Leu Ser STOP Trp	G
C	Leu Pro His Arg	U
C	Leu Pro His Arg	C
C	Leu Pro Gln Arg	A
C	Leu Pro Gln Arg	G
A	Ile Thr Asn Ser	U
A	Ile Thr Asn Ser	C
A	Ile Thr Lys Arg	A
A	Met Thr Lys Arg	G
G	Val Ala Asp Gly	U
G	Val Ala Asp Gly	C
G	Val Ala Glu Gly	A
G	Val Ala Glu Gly	G

[a]Codon UGA can also code for selenocysteine (Sec) under specific circumstances

senescence. Some of these may be evolutionarily conserved across species, but relevant to human health. Mutations and alterations in several of these genomic elements are linked to a broad range of medical conditions. A detailed description of the human genome is beyond the scope and remit of this chapter (see Further Reading resources).

1.3 The Mitochondrial Genome: Structure and Function

The mitochondrial genome is very different from the nuclear genome (Fig. 1.5). In many respects, it has more in common with bacterial genomes than the eukaryotic nuclear genome. Apart from the mitochondrial genome, a number of nuclear genes encode the great majority of mitochondrial proteins. Although the mitochondrial genome is very small compared to its nuclear counterpart, because there are many copies, mtDNA often makes up 1% or so of total cellular DNA.

As in bacteria, the mitochondrial genome is circular and closely packed with genes. There are no introns and little inter-genic non-coding DNA. Mitochondrial genes overlap on the same strand, using the same template but read in different reading frames. Twenty-four of the 37 genes specify functional RNAs (two ribosomal

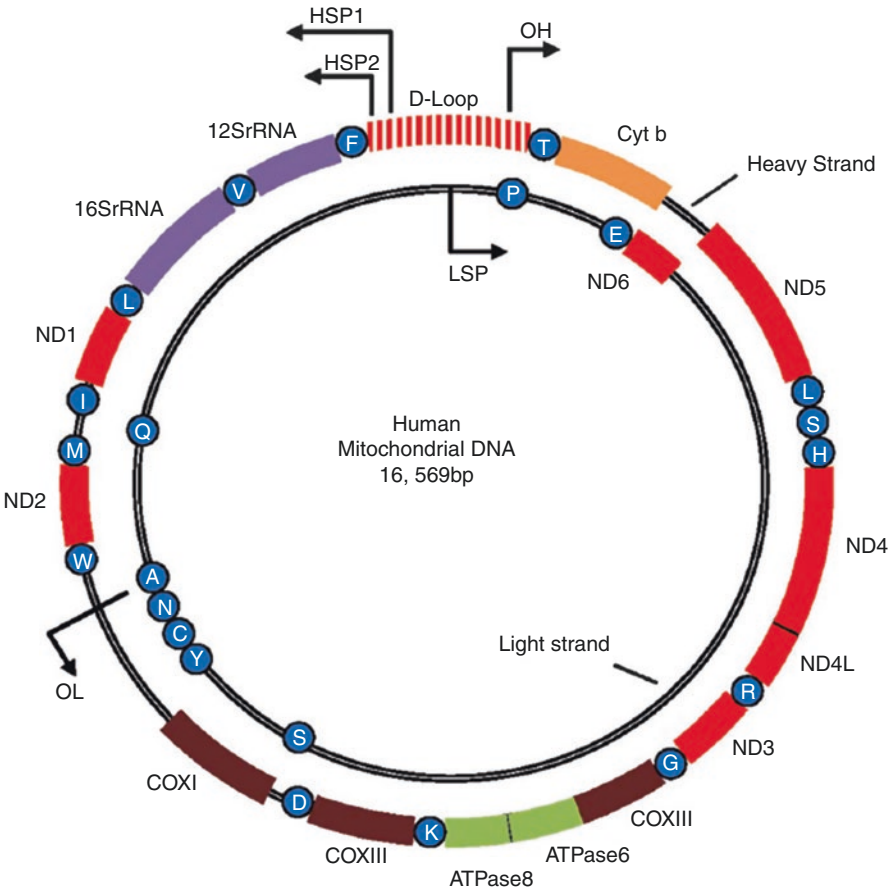

Fig. 1.5 The mitochondrial genome- note no introns; all circular compact mtDNA molecule is compact with coding stands; bulk of the mtDNA codes for the synthesis of transfer RNA (tRNA), ribosomal RNA (rRNA), ATPase and respiratory enzymes