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GENOME-SEQUENCE, ZYGOTE, DIFFERENTIATION OF EMBRYONIC STEM CELLS INTO STRUCTURALLY AND FUNCTIONALLY DIFFERENT SPECIALIZED BODY CELLS IN HUMANS: THERE IS NO "JUNK DNA" AT ALL IN THE HUMAN GENOME!!!!

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ABSTRACT: *About 250 specialized cell types are organized into tissues, organs, and organsystems in the body of humans. Differentiation of cells both in structure & function generally depends on* ***gene expression*** *rather than on any changes in the nucleotide sequence of the cell's genome. The key objective of this paper was to* ***verify*** *that no "junk DNA" at all in the human genome and to* ***confirm*** *the fact that the synthesizer of generations of Homo sapiens & of all other genomic-things is the* ***Genome****. The cell types in a multicellular organism become different from one another because they synthesize and accumulate different sets of RNA and protein molecules. They generally do this without altering the sequence of their DNA with the exception of B & T lymphocytes in the immune system. Differentiation occurs because specific genes in each cell are turned on and off in complex regulated pattern. A stem cell is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. The stem cells derived from a zygote are described as:-* ***totipotent***, ***pluripotent***, ***multipotent***, *and* ***oligopotent*** *stem cells. In contrast, a* ***unipotent cell*** *is fully specialized and can only reproduce to generate more of its own specific cell type. The primary mechanism by which genes are turned "on" or "off" is through transcription factors. A transcription factor is one of a class of proteins that bind to specific genes on the DNA molecule and either promote or inhibit their transcription. Transcription factors regulate gene expression. Transcription factors affect the binding of RNA polymerase to a particular gene on the DNA molecule. Researchers have recently developed* ***induced pluripotent*** *stem cells (iPSCs) from human adult stem cells. The induced pluripotent stem*

cells do function like embryonic stem cells. Non-coding RNAs are a group of RNA transcripts that do not necessarily code for proteins instead they perform the task of regulatory functions. The science of genomic-things is superior to all branches of natural science because the scientist himself, who creates all other nonbiological sciences, is a genomic-thing and belongs to biological sciences. The science of genomic-things is a superscience being the science of priority to invest in. In the automatic functional & structural performance of human genome, every component of it is indispensably useful and none of it is junk DNA at all!! 100% of genome's components, in all species of genomic-things from biological viruses up to humans, are unavoidably useful in the task of synthesizing the individuals & populations of its species in different ecosystems on Earth let alone those of human genome!!!! The genome synthesizes genomic-things & their products using:- ***proteins*** *(structural & functional) translated from its transcripts, and its* ***transcripts*** *directly without translating. Biological sciences are brought up to the status of* ***superscience*** *(the science of genomic-things) by* ***Feleke's Genome Model*** *of genomic-things. Scientists of biological sciences are authentically called* ***superscientists*** *because biological sciences which are their fields of study have been spectacularly developed to the status of* ***superscience****. Establishing a* ***Global Center of Superscience (GCS)*** *is crucial.*

KEYWORDS: Genome, Differentiation, Stem cell, embryonic stem cell, Non-coding RNA, Transcription factors, Gene expression

INTRODUCTION

●a variety of specialized cell types (over 250 types in humans) are organized into tissues, organs, and organ systems.

●The human *IGH* locus contains 66 rearrangeable V_H, 27 D_H, and 6 J_H gene segments that can be involved in rearrangements in B cells to form a VDJ_H exon.

●The different cell types in a multicellular organism differ dramatically in both structure and function. If we compare a mammalian neuron with a lymphocyte, for example, the differences are so extreme that it is difficult to imagine that the two cells contain the same genome. For this reason, and because cell differentiation is often irreversible, biologists originally suspected that genes might be selectively lost when a cell differentiates. It is now

Known that cell differentiation generally depends on changes **in gene expression**

rather than on any changes in the nucleotide sequence of the cell's genome[1-4].

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Review

●The cell types in a multicellular organism become different from one another because they synthesize and accumulate different sets of RNA and protein molecules. They generally do this without altering the sequence of their DNA with the exception of B & T lymphocytes in the immune system. Evidence for the preservation of the genome during cell differentiation comes from a classic set of experiments in frogs.

The process by which committed cells acquire the structures and functions of highly specialized cells:

●Differentiation occurs because specific genes in each cell are turned on and off in a complex, regulated pattern. The different structures of these specialized cells allow them to perform specific functions within the body [4].

●A complex organism such as a human develop from a single cell—a fertilized egg—into the vast array of cell types such as nerve cells, muscle cells, and epithelial cells that characterize the adult. Throughout development and adulthood, the process of cellular differentiation leads cells to assume their final morphology (structure) and physiology (function). Differentiation is the process by which unspecialized cells become specialized to carry out distinct functions.

●A **stem cell** is an unspecialized cell that can divide without limit as needed and can, under specific conditions, differentiate into specialized cells. Stem cells are divided into several categories according to their potential to differentiate. The first embryonic cells that arise from

the division of the zygote are the ultimate stem cells; these stems cells are described as **totipotent** because they have the potential to differentiate into any of the cells needed to enable an organism to grow and develop[5]. The embryonic cells that develop from totipotent stem cells and are precursors to the fundamental tissue layers of the embryo are classified as pluripotent. A **pluripotent** stem cell is one that has the potential to differentiate into any type of human tissue but cannot support the full development of an organism. These cells then become slightly more specialized, and are referred to as multipotent cells. A **multipotent** stem cell has the potential to differentiate into different types of cells within a given cell lineage or small number of lineages, such as a red blood cell or white blood cell. Finally, multipotent cells can become further specialized oligopotent cells. An **oligopotent** stem cell is limited to becoming one of a few different cell types. In contrast, a **unipotent** cell is fully specialized and can only reproduce to generate more of its own specific cell type [5].

●Stem cells are unique in that they can also continually divide and regenerate new stem cells instead of further specializing. There are different stem cells present at different stages of a human's life. They include the embryonic stem cells of the embryo, fetal stem cells of the fetus, and adult stem cells in the adult. One type of adult stem cell is the epithelial stem cell, which gives rise to the keratinocytes in the multiple layers of epithelial cells in the epidermis of skin. Adult bone marrow has three distinct types of stem cells: 1) hematopoietic stem cells, which give rise to red blood cells, white blood cells, and platelets; 2) endothelial stem cells, which give rise to the endothelial cell types that line blood and lymph vessels; and 3) mesenchymal stem cells, which give rise to the different types of muscle cells.

●When a cell differentiates (becomes more specialized), it may undertake major changes in its size, shape, metabolic activity, and overall function. Because all cells in the body, beginning with the fertilized egg, contain the same DNA, how do the different cell types come to be so different? The answer is analogous to a movie script. The different actors in a movie all read from the same script, but each of them reads only his or her own part of the script. Similarly, all cells contain the same full complement of DNA, but each type of cell only "reads" the portions of DNA that are relevant to its own function. In biology, this is referred to as the unique genetic expression of each cell. In order for a cell to differentiate into its specialized form and function, it needs only to manipulate those genes (and thus those proteins) that will be expressed, and not those that will remain silent. The primary mechanism by which genes are turned "on" or "off" is through transcription factors. A **transcription factor** is one of a class of proteins that bind to specific genes on the DNA molecule and either promote or inhibit their transcription.

●Transcription Factors Regulate Gene Expression. While each body cell contains the organism's entire genome, different cells regulate gene expression with the use of various transcription factors. Transcription factors affect the binding of RNA polymerase to a particular gene on the DNA molecule [2].

●Adult stem cells, which exist as a small subset of cells in most tissues, keep dividing and can differentiate into a number of specialized cells generally formed by that tissue. These cells enable the body to renew and repair body tissues.

●Researchers have recently developed **induced pluripotent stem cells** (iPSCs) from mouse and human adult stem cells. These cells are genetically reprogrammed multipotent adult cells that function like embryonic stem cells; they are capable of generating cells characteristic of all three germ layers (ectoderm, mesoderm, and endoderm lines).

●Because of their capacity to divide and differentiate into specialized cells, stem cells offer a potential treatment for diseases such as diabetes and heart disease. Cell-based therapy refers to

treatment in which stem cells induced to differentiate in a growth dish are injected into a patient to repair damaged or destroyed cells or tissues.

●Patient's gamete fertilized with a gamete of genetically closest relative as a test-tube zygote growing into an invitro embryo for embryonic stem cell to inject into the needy client (patient) can effectively solve the risk of graft rejection by the patient's immune system.

●Approximately 95% of human transcripts are thought to be non-coding RNAs. The regulatory functions of long non-coding RNAs (lncRNAs) are under active investigation by several groups and have been recently reviewed. Studies in a variety of organisms over the last two decades suggest that RNA molecules contain many more *cis*- and *trans*-regulatory functions than previously thought. Although initially lncRNAs were thought to function strictly as RNAs and not code for proteins, recent studies have showed that many previously annotated non-coding RNAs can recruit ribosomes and encode short peptides. In addition, emerging evidence suggests that even protein coding mRNAs can have structural and/or regulatory functions independent of the protein they encode.

●Coding and non-coding transcripts can function as to bind miRNAs and alleviate the repressive activity of miRNAs on the target mRNAs. Such RNAs that regulate the activity of other RNAs by directly competing for miRNA binding are named as competing endogenous RNAs (ceRNAs) and any perturbation in their levels can lead to disease states.

●Bi-functional RNAs which combine protein-coding and noncoding functions in a single RNA molecule do exist [6].

●The antigen receptor loci of B and T lymphocytes exhibit a unique mechanism of control amongst the genes of multicellular organisms. The production of functional immunoglobulin (Ig) and T cell receptor (TCR) genes is accomplished through a tightly regulated process of recombination. Variable (V), diversity (D) and joining (J) gene segments of antigen receptor loci are assembled into a functional coding unit by a series of site-specific recombination events mediated by the products of recombination activating gene (RAG)1 and RAG2 [1]. Recombination is targeted to specific sites by the recombination signal sequences (RSS), which flank the gene segments. RSS motifs consist of a conserved heptamer (CACAGTG) separated from a conserved nonamer (ACAAAAACC) by a spacer of variable sequence of either 12 or 23 base pairs (bp). Recombination occurs between an RSS with a 12-bp spacer (RSS12) and an RSS with a 23-bp spacer (RSS23) and the intervening DNA is either deleted or inverted depending upon the orientation of the two signals. Double strand breaks introduced at the RSS motifs by the RAG proteins are then resolved by non-homologous end joining. Two products are generated, a signal

joint in which the RSS motifs are joined and a coding joint in which the gene segments are joined [1].

●**V(D)J recombination** is the unique mechanism of genetic recombination that occurs only in developing lymphocytes during the early stages of T and B cell maturation. It involves somatic recombination, and results in the highly diverse repertoire of antibodies/immunoglobulins and T cell receptors (TCRs) found in B cells and T cells, respectively. The process is a defining feature of the adaptive immune system [1].

●Every person has two copies of each gene, one inherited from each parent. Most genes are the same in all people, but a small number of genes (less than 1 percent of the total) are slightly different between people. Alleles are forms of the same gene with small differences in their sequence of DNA bases. These small differences contribute to each person's unique physical features [1].

●Control of genome activity by mechanisms that specify which genes are transcribed and which are silent is very important [4].

●**Permanent and Semipermanent Changes in Genome Activity.** Transient changes in genome activity are reversible if the gene expression pattern reverts to its original state when the external stimulus is removed or replaced by a contradictory stimulus. In contrast, the permanent and semipermanent changes in genome activity that underlie cellular differentiation must persist for long periods, and ideally should be maintained even when the stimulus that originally induced them has disappeared. We will look at three mechanisms:

►Changes resulting from physical rearrangement of the genome,

►Changes due to alteration in chromatin structure, and

►Changes maintained by feedback loops.

●Genome rearrangements are responsible for immunoglobulin and T-cell receptor diversities.

In vertebrates there are two striking examples of the use of DNA rearrangements to achieve permanent changes in genome activity. These two examples, which are very similar, are responsible for the generation of immunoglobulin and T-cell receptor diversities.

Immunoglobulins and T-cell receptors are proteins that are synthesized by B and T lymphocytes, respectively. Both types of protein become attached to the outer surfaces of their cells, and immunoglobulins are also released into the bloodstream. The proteins help to protect the body against invasion by bacteria, viruses and other unwanted substances by binding to these antigens, as they are called. During its lifetime, an organism could be exposed to any number of a vast range

of antigens, which means that the immune system must be able to synthesize an equally vast range of immunoglobulin and T-cell receptor proteins. In fact, humans can make approximately 10^8 different immunoglobulin and T-cell receptor proteins. But there are only 3.5×10^4 genes in the human genome, so where do all these proteins come from? [4]. As a B lymphocyte develops, the immunoglobulin loci in its genome undergo rearrangements [4]..

Concrete evidences about the fact that 95% of human genome transcripts are not "junk DNA", being essential for structural & critical regulatory functions:

1.●Genes: A typical protein-coding gene is first copied into RNA as an intermediate in the manufacture of the final protein product. In other cases, the RNA molecules are the actual functional products, as in the synthesis of ribosomal RNA and transfer RNA. Some RNAs known as ribozymes are capable of enzymatic function, and microRNA has a regulatory role. The DNA sequences from which such RNAs are transcribed are known as non-coding RNA genes (introns) [4].

2.●Non-coding RNAs are a group of RNA transcripts that do not necessarily code for protein products, instead they perform the task of regulatory functions [7].

3.● a DNA's introns can be much larger than its exons. Regulatory regions can even be on entirely different chromosomes and operate *in trans* to allow regulatory regions on one DNA molecule to come in contact with target genes on another DNA molecule [7].

6.●The genome is the total genetic material of an organism and includes both the genes and non-coding sequences [4].

7.●Non-coding RNAs (ncRNAs) have been implicated in the epigenetic marking of many genes. Short regulatory ncRNAs, including miRNAs, siRNAs, piRNAs and sncRNAs as well as long ncRNAs such as Xist and Air regulate mechanisms of chromatin marking and RNA editing [7].

8.●Non-coding RNAs (nc RNAs) comprise a variety of RNA species that do not encode proteins and were thought for a long time to be part of the so-called "junk DNA." Recent publications have, however, shown that several of these nc RNAs have profound effects in the regulation of transcription and translation and, therefore, play major roles in biological processes in health and disease. Non-coding RNAs include small ncRNAs that are normally less than 200 bases, such as microRNA (miRNA), short interfering RNA (siRNA), and piwi-interacting RNA (piRNA), as well as long ncRNA (lincRNA) and also long antisense RNA. Among these micromolecules, miRNAs (approximately 22 nucleotides long) have been studied the most. A single miRNA controls hundreds of target genes, so that miRNAs modulate a variety of biological functions, including embryogenesis, cell differentiation, tissue homeostasis, carcinogenesis, toxicity, and viral infections [7].

9.●A **non-coding RNA** (ncRNA) is a functional RNA molecule that is transcribed from DNA but not translated into proteins. **Epigenetic** related ncRNAs include miRNA, siRNA, piRNA and lncRNA. In general, ncRNAs function to regulate gene expression at the transcriptional and post-transcriptional level. Those ncRNAs that appear to be involved in epigenetic processes can be divided into two main groups; the short ncRNAs (<30 nucleotides) and the long ncRNAs (>200 nucleotides). The three major classes of short non-coding RNAs are microRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs). Both major (that is, short & long) groups are shown to play a role in heterochromatin formation, **histone modification**, **DNA methylation** targeting, and gene silencing [7].

10.Short ncRNAs: *MicroRNAs (miRNA)* generally bind to a specific target messenger RNA with a complementary sequence to induce cleavage, or degradation or block translation. This may be done in the context of a feedback mechanism that involves chromosome methylation. For example, miRNA genes mir-127 and mir-136 were found to be involved in regulating the genetic imprinting of Rtl1, a key gene involved in placenta formation in mice. Methylation of a specific region in the paternal DNA molecule results in expression of Rtl1. If the DNA molecule is not methylated, as on the maternal DNA molecule, mir-127 and mir-136 are produced and bind to the Rtl1 transcript and induce degradation. Lack of Rtl1 protein expression due to improper epigenetic modifications can result in fetal death in mice. *Short interfering RNAs (siRNA)* function in a similar way as miRNAs to mediate post-transcriptional gene silencing (PTGS) as a result of mRNA degradation. In addition to this function, siRNAs have also been shown to induce heterochromatin formation via an RNA-induced transcriptional silencing (RITS) complex which when bound to siRNA promotes H3K9 methylation and chromatin condensation. *Piwi-interacting RNAs (piRNA)* are so named due to their interaction with the piwi family of proteins. The primary function of these RNA molecules involves chromatin regulation and suppression of transposon activity in germline and somatic cells. PiRNAs that are antisense to expressed transposons target and cleave the transposon in complexes with PIWI-proteins. This cleavage generates additional piRNAs which target and cleave additional transposons. This cycle continues to produce an abundance of piRNAs and augment transposon silencing [7].

11. Long ncRNAs: Many lncRNAs can complex with chromatin-modifying proteins and recruit their catalytic activity to specific sites in the genome, thereby modifying chromatin states and influencing gene expression.1) The majority of non-coding RNA transcripts belong to the group lncRNAs. Long ncRNAs function in chromatin remodeling, transcriptional regulation, post-transcriptional regulation, and as precursors for siRNAs. 2) One particular subgroup of lncRNAs, the large intergenic non-coding RNAs (lincRNAs), has been associated with chromatin modifying complexes which can target specific genomic loci to promote specific epigenetic states. 3) One widely known example of lincRNA is the role of X-inactive specific transcript gene (Xist), in X-DNA inactivation (XDI). This process involves two lncRNAs; Xist and its antisense transcript Tsix, a negative regulator of Xist. Prior to differentiation, Xist and Tsix are actively transcribed due to H3K4 dimethylation of the Xist gene. In this state XDI is a random event. Upon

differentiation, Xist expression is elevated resulting in Xist RNA coating the future inactive X DNA molecule which triggers extensive histone methylation and DNA molecule inactivation [8].

12.●Bi-functional RNAs which combine protein-coding and noncoding functions in a single RNA molecule do exist [4].

13.●Coding and non-coding transcripts can function to bind miRNAs and alleviate the repressive activity of miRNAs on the target mRNAs. Such RNAs that regulate the activity of other RNAs by directly competing for miRNA binding are named as competing endogenous RNAs (ceRNAs) and any perturbation in their levels can lead to disease states.

14.●*The MyoD transcription activator*, which is involved in muscle development, is one of the best understood examples of cellular differentiation in vertebrates. A cell becomes committed to becoming a muscle cell when it begins to express the *myoD* gene.

15.●The cell types in a multicellular organism become different from one another because they synthesize and accumulate different sets of RNA and protein molecules. They generally do this without altering the sequence of their DNA. Evidence for the preservation of the genome during cell differentiation comes from a classic set of experiments in frogs. When the **nucleus** of a fully differentiated frog cell is injected into a frog **egg** whose nucleus has been removed, the injected donor nucleus is capable of directing the recipient egg to produce a normal tadpole.

16.●By the criteria mentioned above, the DNA molecules contained in chromosome sets of all differentiated cells in the human body appear to be identical. Furthermore, comparisons of the genomes of different cells based on recombinant DNA technology have shown, as a general rule, that the changes in gene expression that underlie the development of multicellular organisms are not accompanied by changes in the DNA sequences of the corresponding genes. The only exception to what is stated above about DNA sequences is the reprogrammed DNA rearrangements in B & T lymphocytes to generate the diversity of the immune system of mammals [4].

17. ●As a first step in understanding cell differentiation, differences can be seen between any one cell type and another and based on this the following 3 statements can be made.

a). Many processes are common to all cells, any two cells in a single organism therefore have many proteins in common. These include the structural proteins of chromosomes, RNA polymerase, DNA repair enzymes, ribosomal proteins, enzymes involved in the central reactions of metabolism, and many of the proteins that form the cytoskeleton.

b). Some proteins are abundant in the specialized cells in which they function and cannot be detected elsewhere, even by sensitive tests. Hemoglobin, for example, can be detected only in red blood cells.

c). Studies of the number of different mRNA suggest that, at any one time, a typical human cell expresses approximately 10,000-20,000 of its approximately 30,000 genes. When the patterns of mRNAs in a series of different human cell lines are compared, it is found that the level of expression of almost of every active gene varies from one cell type to another. A few of these differences are striking like that of hemoglobin noted above but most are much more subtle. The patterns of mRNA abundance (determined using DNA microarray are so characteristic of cell type that they can be used to type human cancer cells of uncertain tissue origin [4].

18.●Gene Expression Can Be Regulated at Many of the Steps in the Pathway from DNA to RNA to Protein: If differences among the various cell types of an organism depend on the particular genes that the cells express, at what level is the control of gene expression exercised? There are many steps in the pathway leading from DNA to protein, and all of them can in principle be regulated. Thus a cell can control the proteins it makes by (1) controlling when and how often a given gene is transcribed (transcriptional control), (2) controlling how the RNA transcript is spliced or otherwise processed (RNA processing control), (3) selecting which completed mRNAs in the cell nucleus are exported to the cytosol and determining where in the cytosol they are localized (RNA transport and localization control), (4) selecting which mRNAs in the cytoplasm are translated by ribosomes (translational control), (5) selectively destabilizing certain mRNA molecules in the cytoplasm (mRNA degradation control), or (6) selectively activating, inactivating, degrading, or compartmentalizing specific protein molecules after they have been made (protein activity control).

19.●The genome of a cell contains in its DNA sequence the information to make many thousands of different protein and RNA molecules. A cell typically expresses only a fraction of its genes, and the different types of cells in multicellular organisms arise because different sets of genes are expressed. Moreover, cells can change the pattern of genes they express in response to changes in their environment, such as signals from other cells. Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control [4].

20.●a **gene** is a sequence of nucleotides in DNA or RNA that encodes the synthesis of a gene product, either RNA or protein. During gene expression, the DNA is first copied into RNA. The RNA can be directly functional or be the intermediate template for a protein that performs a function [9].

21.● Each gene specifies a particular trait with different sequence of a gene (alleles) giving rise to diferent phenotypes. Most eukaryotic organisms (such as the pea plants Mendel worked on) have two alleles for each trait, one inherited from each parent. Alleles at a locus may

be dominant or recessive; dominant alleles give rise to their corresponding phenotypes when paired with any other allele for the same trait, whereas recessive alleles give rise to their corresponding phenotype only when paired with another copy of the same allele [10].

22.●In sexually reproducing organisms, a specialized form of cell division called meiosis produces cells called gametes or germ cells that are haploid, or contain only one copy of each gene. The gametes produced by females are called eggs or ova, and those produced by males are called sperm. Two gametes fuse to form a diploid fertilized egg (Fig. 14), a single cell that has two sets of genes, with one copy of each gene from the mother and one from the father [10].

23.●Control of genome activity by mechanisms that specify which genes are transcribed and which are silent (turned off or inhibited) is very important [4].

24.●Regulatory_regions of a gene such as enhancers do not necessarily have to be close to the coding sequence on the linear molecule because the intervening DNA can be looped out to bring the gene and its regulatory region into proximity. Similarly, a DNA's introns can be much larger than its exons. Regulatory regions can even be on entirely different DNA molecules and operate *in trans* to allow regulatory regions on one DNA molecule to come in contact with target genes on another DNA molecule [10].

25.●Human genome contains a large number of functional ncRNAs. Highly validated ncRNAs are listed in the long ncRNA Database, representing a new educational wealth in the science of genomic-things [11].

26.●DNA modifications that do not change the DNA sequence can affect gene activity. Chemical compounds that are added to single genes can regulate their activity; these modifications are known as epigenetic changes. The epigenome comprises all of the chemical compounds that have been added to the entirety of one's DNA (genome) as a way to regulate the activity (expression) of all the genes within the genome. The chemical compounds of the epigenome are not part of the DNA sequence, but are on or attached to DNA ("epi-" means above in Greek). Epigenetic modifications remain as cells divide and in some cases can be inherited through the generations. Environmental influences, such as a person's diet and exposure to pollutants, can also impact the epigenome [12].

27.●Epigenetic changes can help determine whether genes are turned on or off and can influence the production of proteins in certain cells, ensuring that only necessary proteins are produced. For example, proteins that promote bone growth are not produced in muscle cells. Patterns of epigenetic modification vary among individuals, different tissues within an individual, and even different cells [12].

28.●A common type of epigenetic modification is called DNA methylation. DNA methylation involves attaching small molecules called methyl groups, each consisting of one carbon atom and

three hydrogen atoms, to segments of DNA. When methyl groups are added to a particular gene, that gene is turned off or silenced, and no protein is produced from that gene [12].

29.●Because errors in the epigenetic process, such as modifying the wrong gene or failing to add a compound to a gene, can lead to abnormal gene activity or inactivity, they can cause genetic disorders. Conditions including cancers, metabolic disorders, and degenerative disorders have all been found to be related to epigenetic errors [13].

30.●Scientists continue to explore the relationship between the genome and the chemical compounds that modify it. In particular, they are studying what effect the modifications have on gene function, protein production, and human health [13].

31.●In opposition to terminally differentiated cells, stem cells can self-renew and give rise to multiple cell types. Embryonic stem cells retain the ability of the inner cell mass of blastocysts to differentiate into all cell types of the body and have acquired in culture unlimited self-renewal capacity [5].

32.●Regulating gene expression. Some non-coding DNA sequences determine the expression levels of various genes and have other functional roles.

A).Transcription factors: Some non-coding DNA sequences determine where transcription factors attach. A transcription factor is a protein that binds to specific non-coding DNA sequences, thereby controlling the flow (or transcription) of genetic information from DNA to mRNA. In other words, Transcription Factors Regulate Gene Expression. While each body cell contains the organism's entire genome, different cells regulate gene expression with the use of various transcription factors. Transcription factors affect the binding of RNA polymerase to a particular gene on the DNA molecule.

B).Operators: An operator is a noncoding segment of DNA to which a repressor binds. A repressor is a DNA-binding protein that regulates the expression of one or more genes by binding to the operator and blocking the attachment of RNA polymerase to the promoter, thus preventing transcription of the genes. This blocking of expression is called repression.

C).Enhancers: An enhancer is a noncoding short region of DNA that can be bound with proteins (trans-acting factors), much like a set of transcription factors, to enhance transcription levels of genes in a gene cluster.

D).Silencers: A silencer is a noncoding region of DNA that inactivates gene expression when bound by a regulatory protein. It functions in a very similar way as enhancers, only differing in the inactivation of genes.

E).Promoters: A promoter is a noncoding region of DNA that facilitates transcription of a particular gene when a transcription factor binds to it. Promoters are typically located near the genes they regulate and upstream of them.

F).Insulators: A genetic insulator is a noncoding boundary element that plays two distinct roles in gene expression, either as an enhancer-blocking code, or rarely as a barrier against condensed chromatin. An insulator in a DNA sequence is comparable to a linguistic word divider such as a comma in a sentence, because the insulator indicates where an enhanced or repressed sequence ends.

G).Forensic anthropology: Police sometimes gather DNA as evidence for purposes of forensic identification. The DNA material in chromosomes is composed of "coding" and "non-coding" regions. The coding regions are known as genes and contain the information necessary for a cell to make proteins. Non-protein coding regions have been referred to as "junk DNA." It is this noncoding DNA region that has been used for scientific investigation of crime with near certainty to identify a person.

H).Telomere: is a noncoding region of DNA with repetitive nucleotide sequences at each end of a chromosome. Telomere protects each end within the chromosome from deterioration, degradation or from fusion with those of neighboring chromosomes. The sequence of nucleotides in telomeres is AGGGTT with complementary DNA strand being TCCCAA.

I).Centromere: is a specialized noncoding sequence of DNA in a chromosome that perfoms a structural function of linking or binding a pair of sister chromatids (a dyad) together.

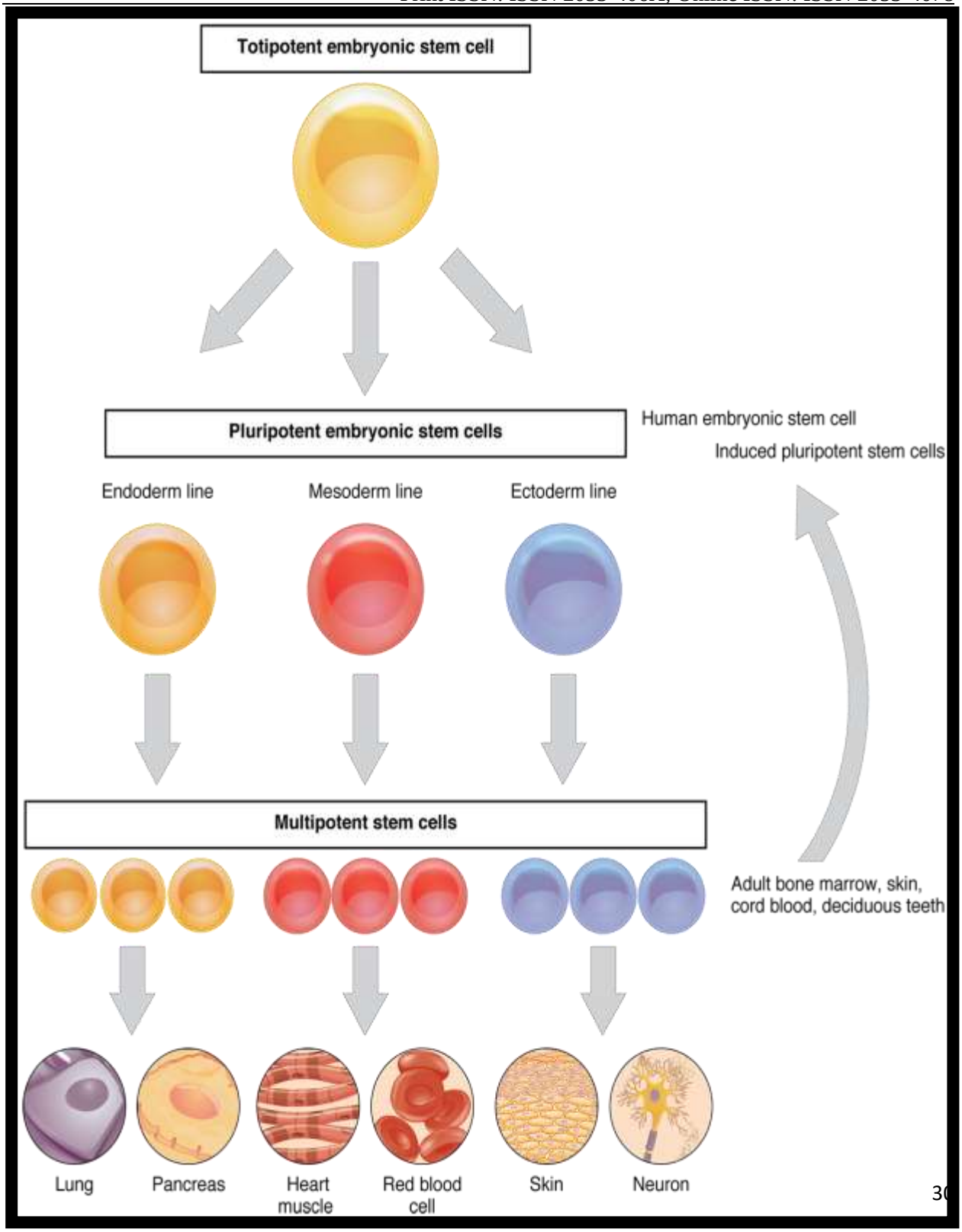

Totipotent embryonic stem cell
Pluripotent embryonic stem cells
Human embryonic stem cell
Induced pluripotent stem cells
Endoderm line
Mesoderm line
Ectoderm line
Multipotent stem cells
Adult bone marrow, skin, cord blood, deciduous teeth
Lung
Pancreas
Heart muscle
Red blood cell
Skin
Neuron

Figure 1: Stages & categories of stem cells in the ontogenical stages of human body.

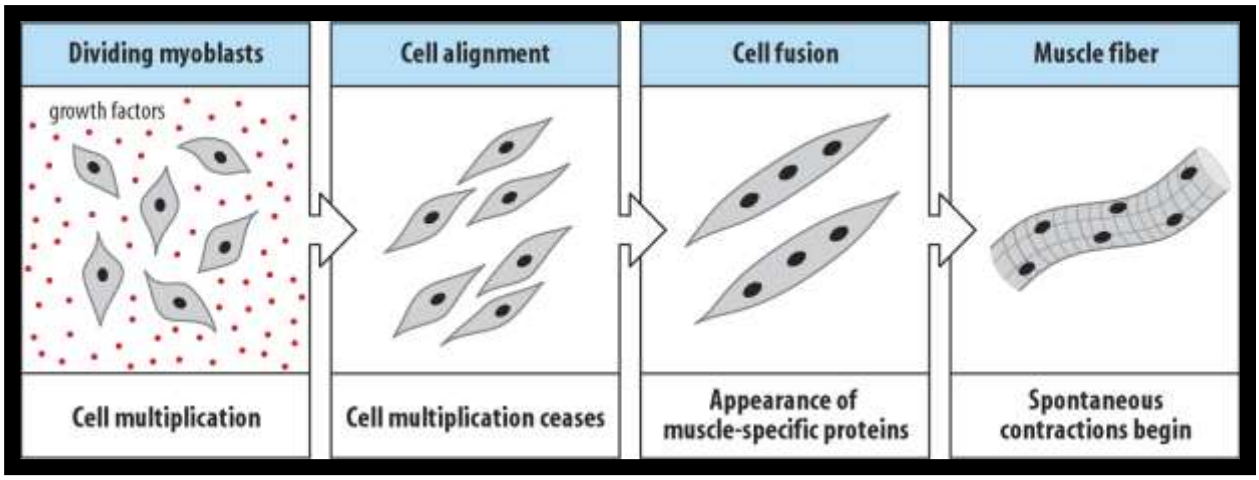


Figure 2: Process of skeletal muscle cell/fiber differentiation, forming a specialized muscle cell.

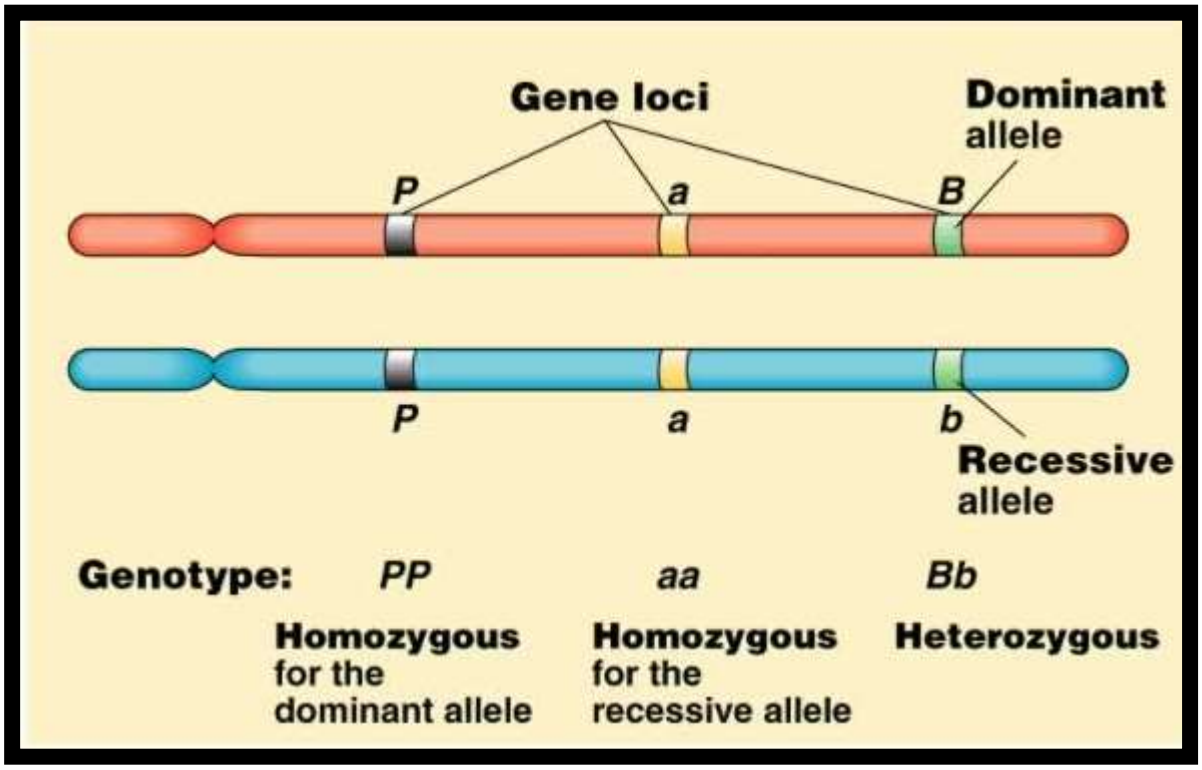


Figure 3: Homologous chromosomes, showing some genotypes.

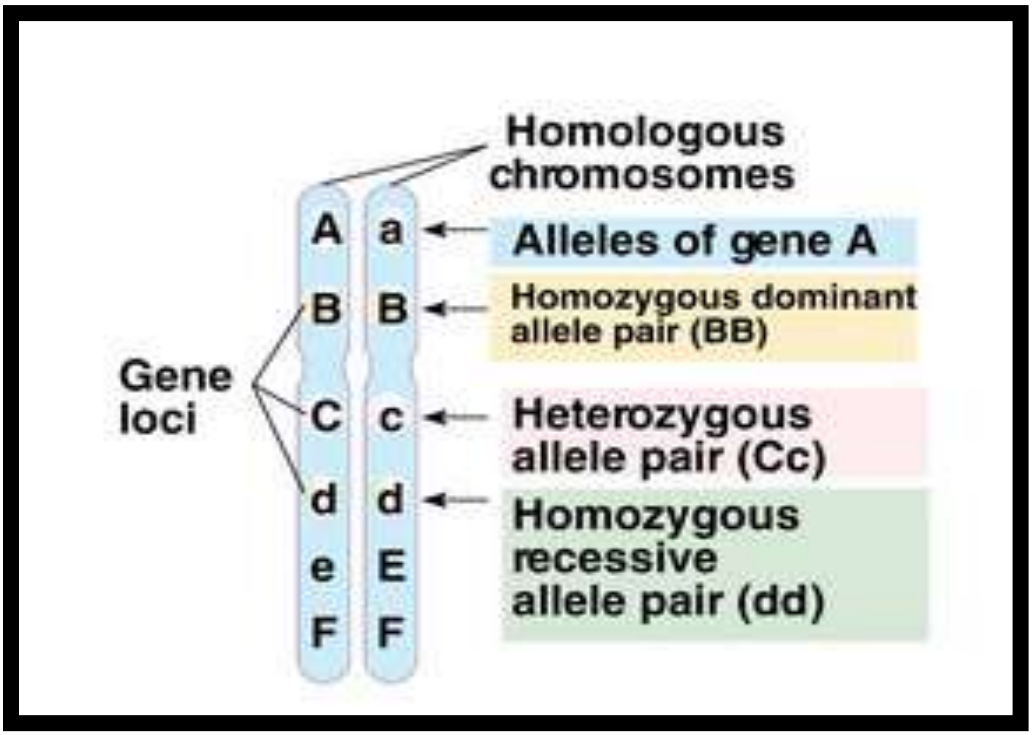
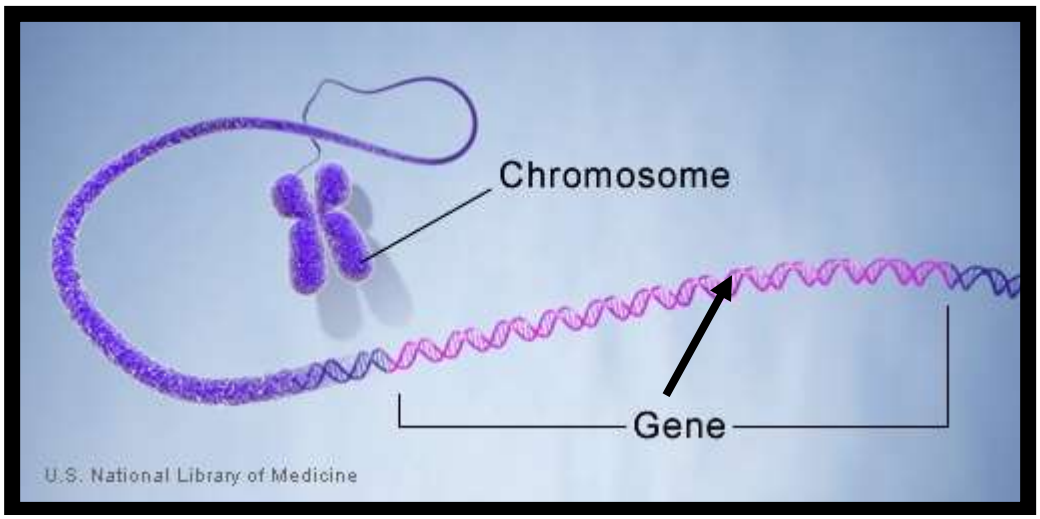


Figure 4: Morphology of a pair of homologous chromosomes with allelic genes loci.



Credit: U.S. National Library of Medicine

Figure 5: Morphology of a pair of homologous chromosomes where from one of them, the DNA molecule is isolated from the associated structural proteins and a gene of it is shown**.**

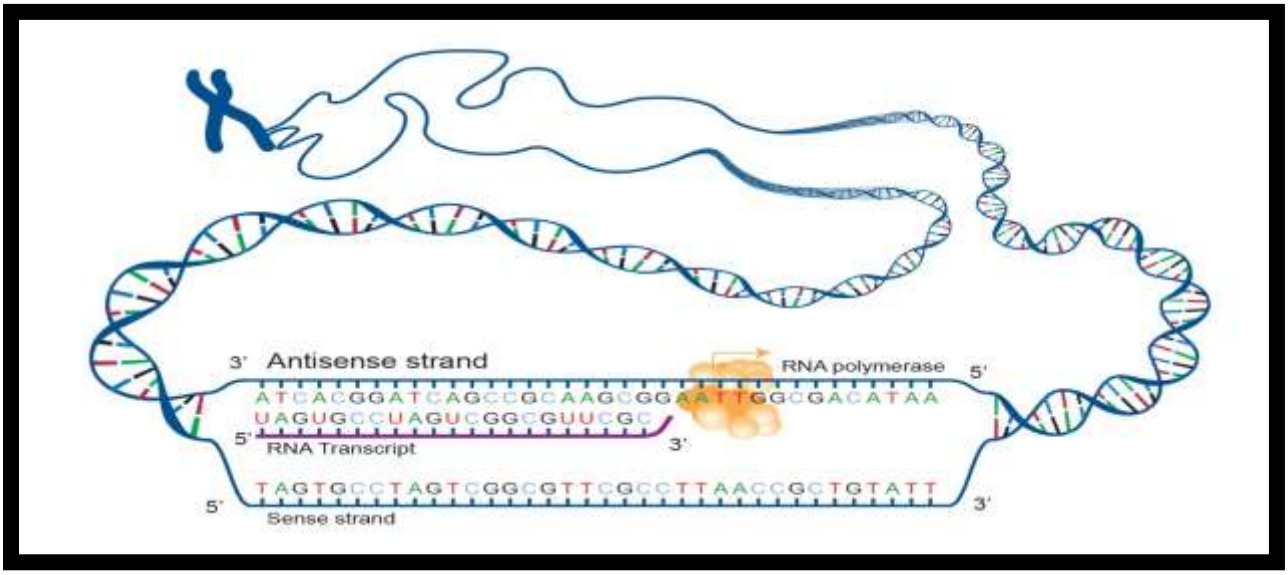


Figure 6: Illustration of transcribing an RNA transcript from a DNA molecule.

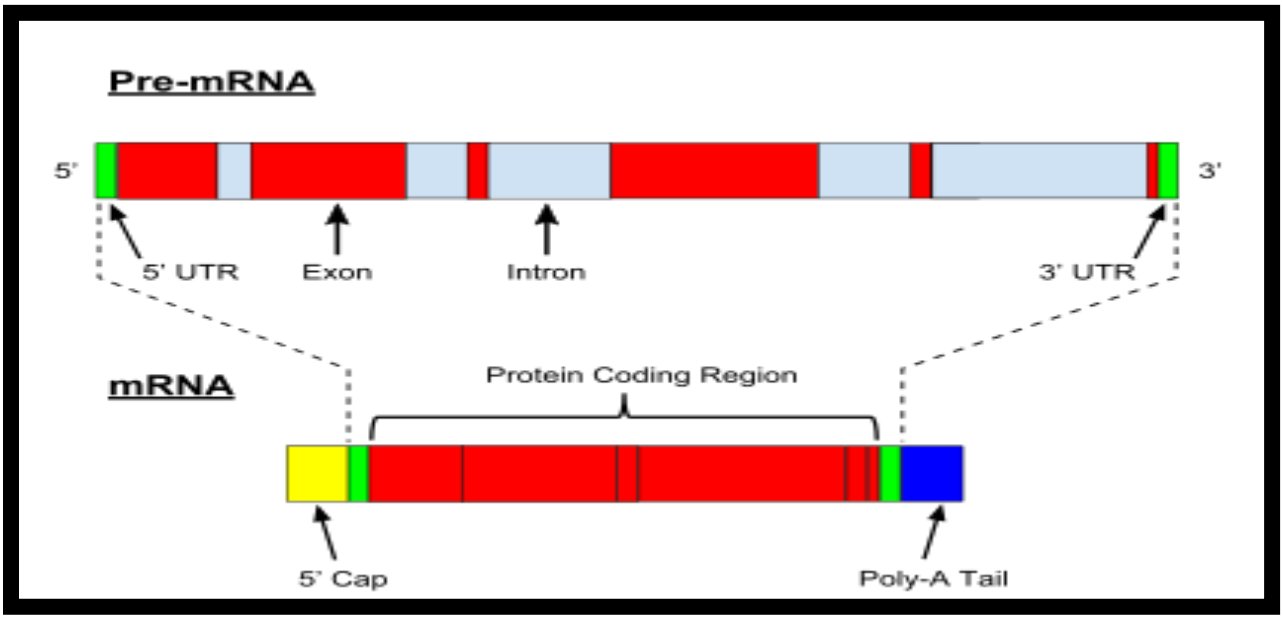


Figure 7: Illustration of an unspliced pre-mRNA precursor, with five introns and six exons (top). After the introns have been removed via splicing, the mature mRNA sequence is ready for translation (bottom).

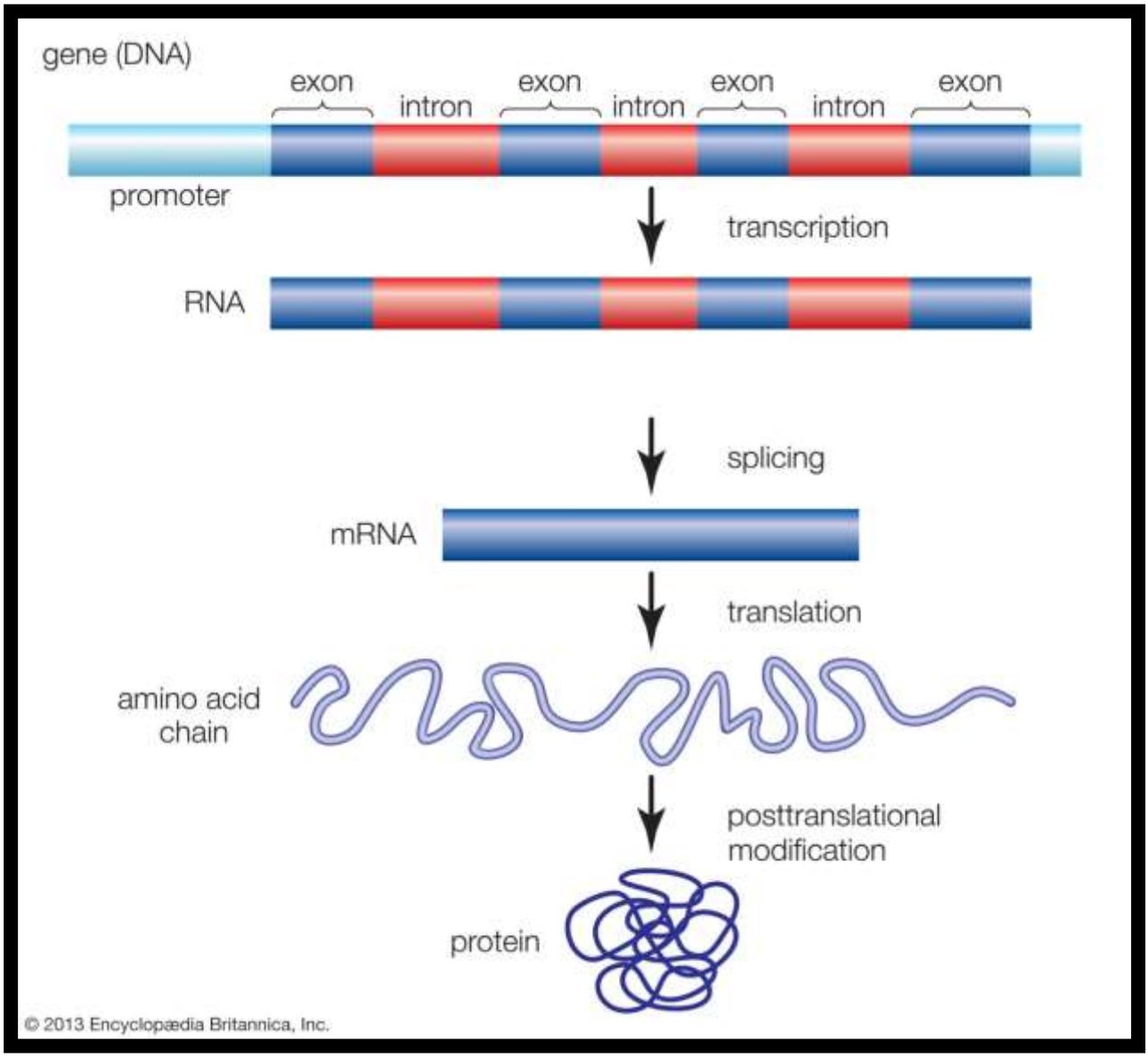


Figure 8: Transcription, splicing, translation, and posttranslational modification.

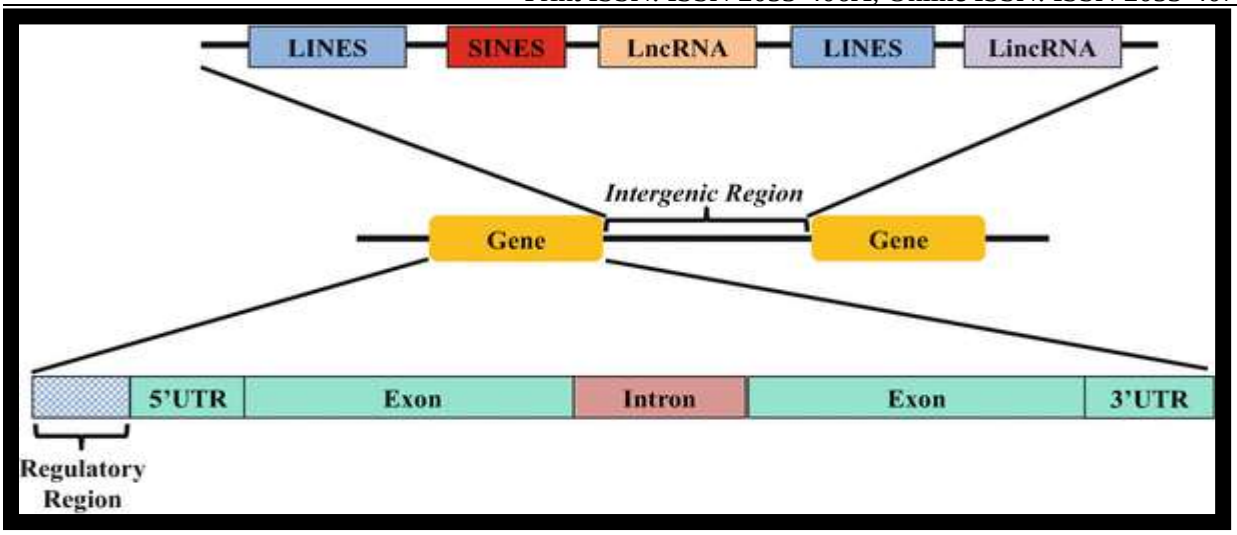


Figure 9: Regulatory region, 5'UTR, Exon, Intron, Exon, 3'UTR.

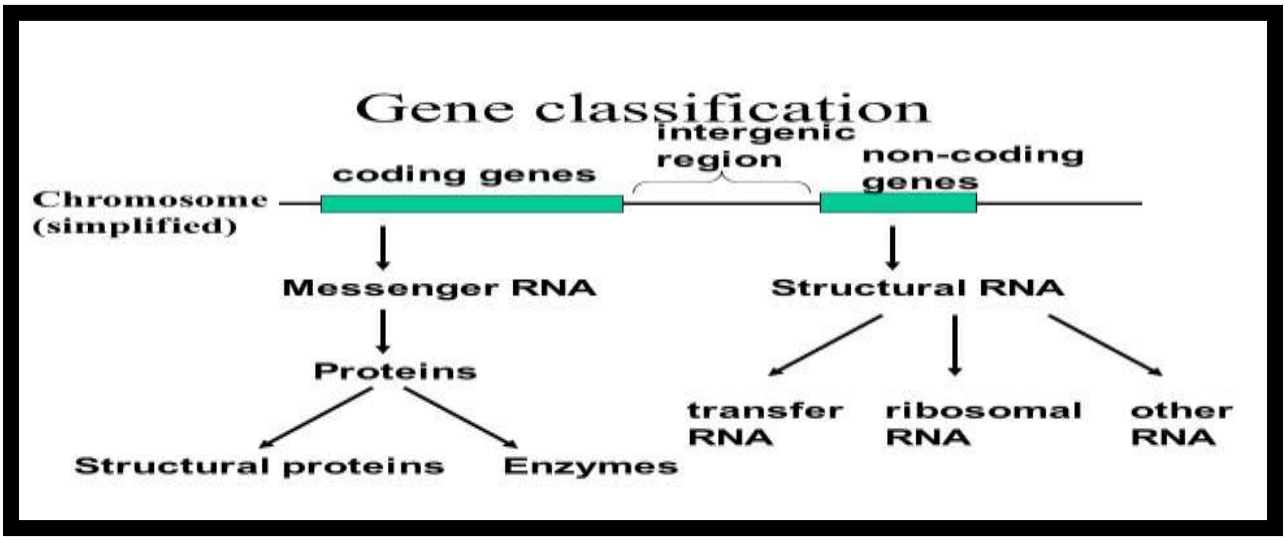


Figure 10: Gene classification and summarized functional products.

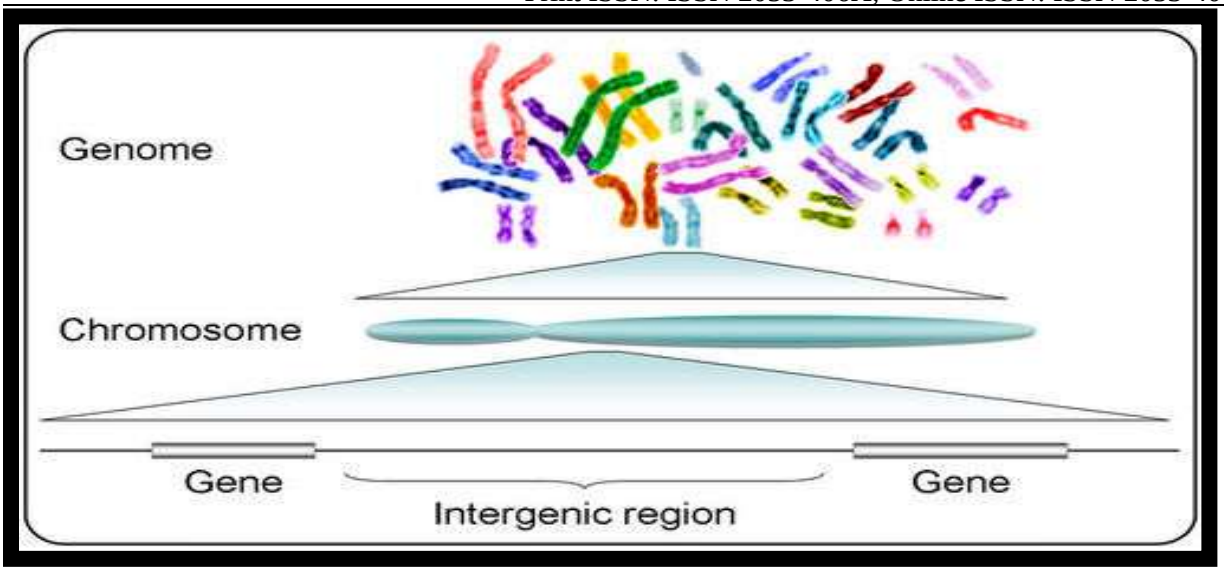


Figure 11: The map of human **Genome**, chromosome, and intergenic region presented by the **Human Genome Project**.

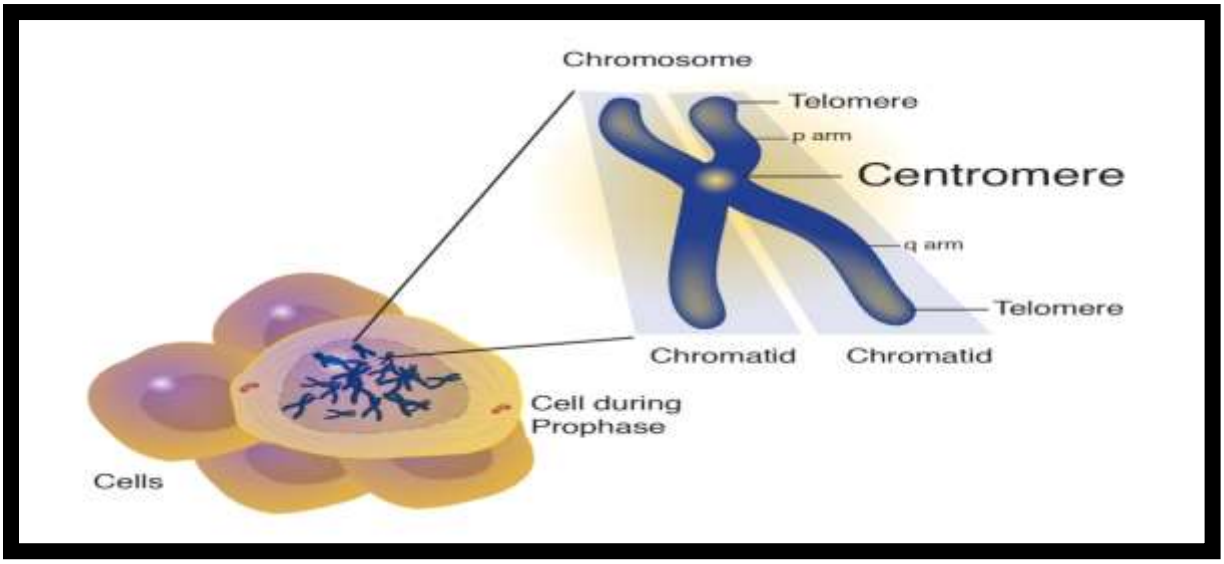


Figure 12: Replication of DNA during cell division. In this picture, it is also called the replication of a chromosome for the DNA is together with its structural proteins including histones & other associated proteins. Each sister chromatid contains one double stranded DNA molecule.

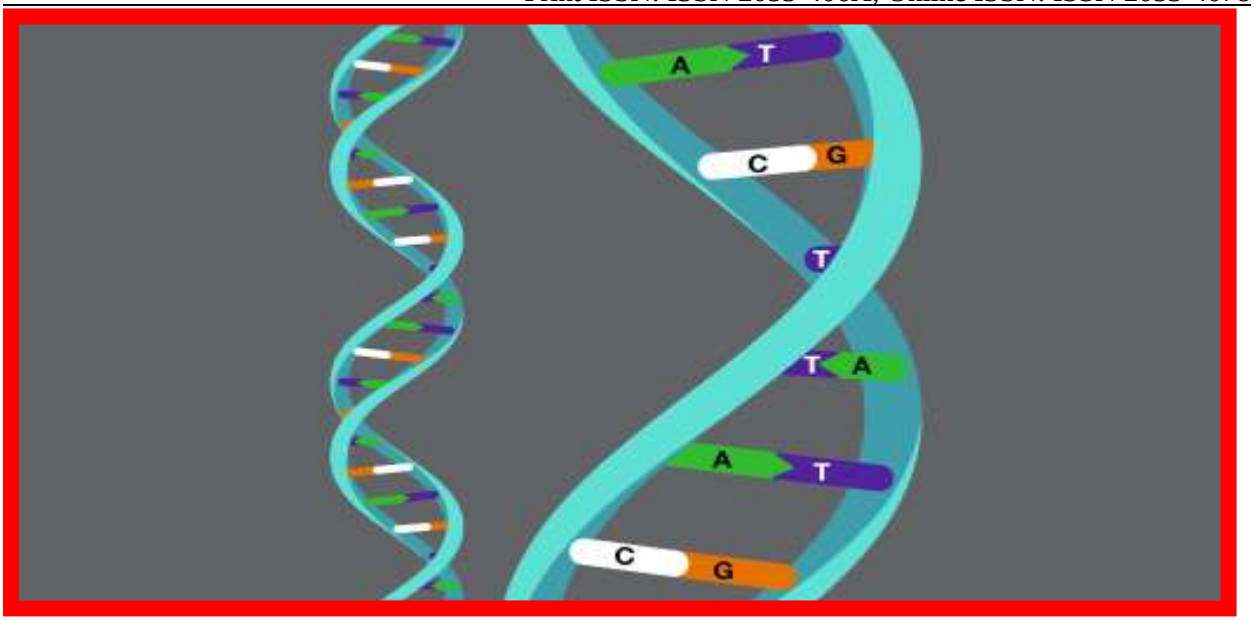


Figure 13: This is what the morphology of a DNA molecule's segments look like when it is isolated from its structural proteins.

When a DNA is not isolated from its structural proteins is known as chromosome. **Telomere** is a region of DNA with repetitive nucleotide sequences at each end of a chromosome. Telomere protects each end of the chromosome from deterioration or from fusion with neighboring chromosomes. The sequence of nucleotides in telomeres is AGGGTT with complementary DNA strand being TCCCAA.

Centromere is a specialized sequence of DNA in a chromosome that links/binds a pair of sister chromatids (a dyad).

Note: Be conscious, chromosomes of a species of genomic-things cannot form or represent the genome of that species but the DNA molecules contained in the chromosomes. If you do not know the difference between chromosomes and the genome, your position of understanding biological sciences (pure biology, medical sciences, agricultural sciences) is in danger of being beating around the bush. Chromosomes are genome plus structural proteins of the genome. Genome of *Homo sapiens* is 46 DNA molecules and not the 46 chromosomes. Each chromosome of a person contains one double stranded DNA molecule [23-28]. It must be clear that the structural proteins (histones & others) associated with DNA molecule in each chromosome are translations of the transcripts (mRNAs) transcribed from the genes of the **genome**!! Genome is the only automatic molecule capable of synthesizing itself and all other body structures as well as molecules including proteins in all genomic-things from biological viruses upto human beings.

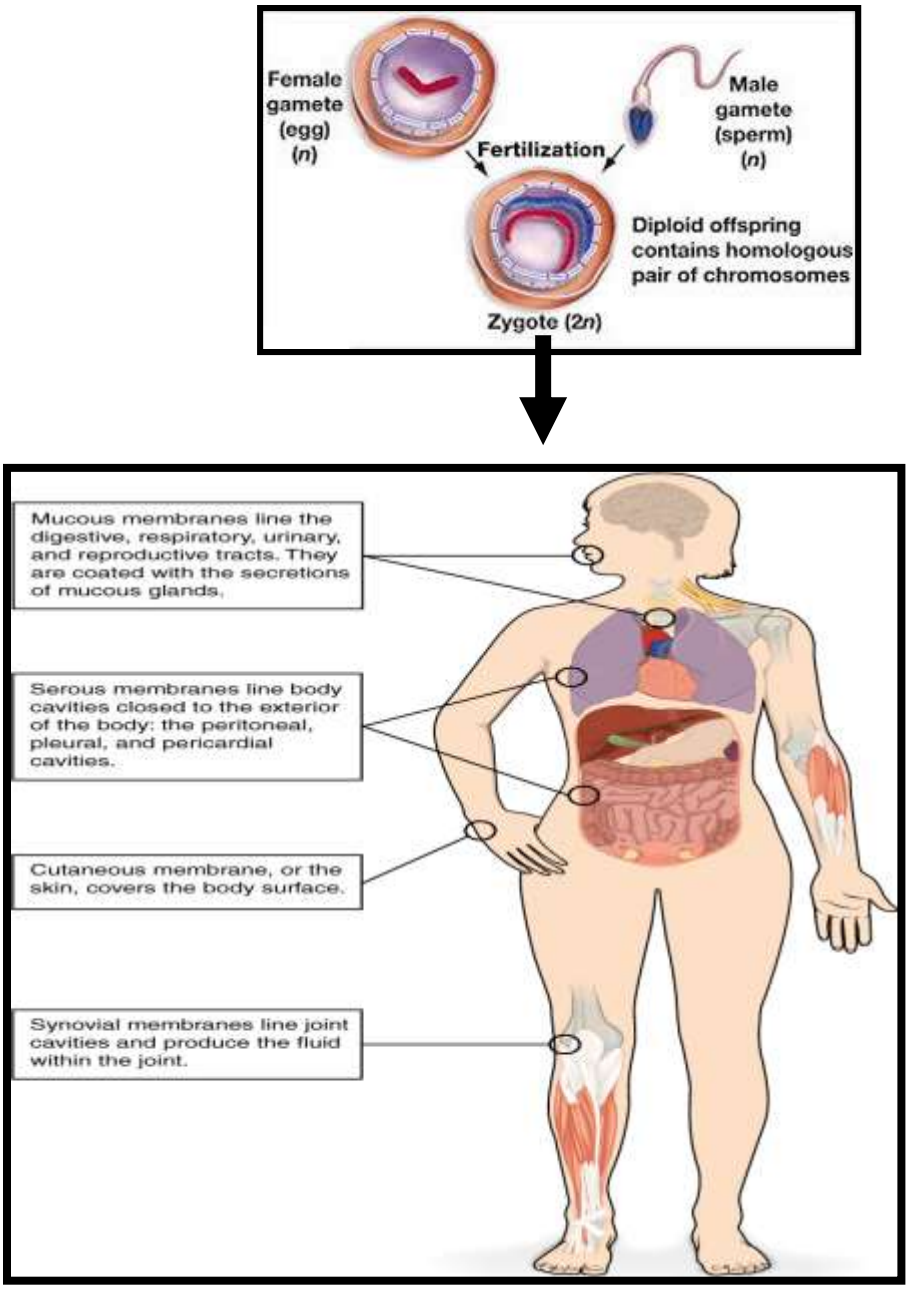


Figure 14: Differentiation of a single-celled human zygote into an adult person composed of about 100 trillion specialized cells!!!!

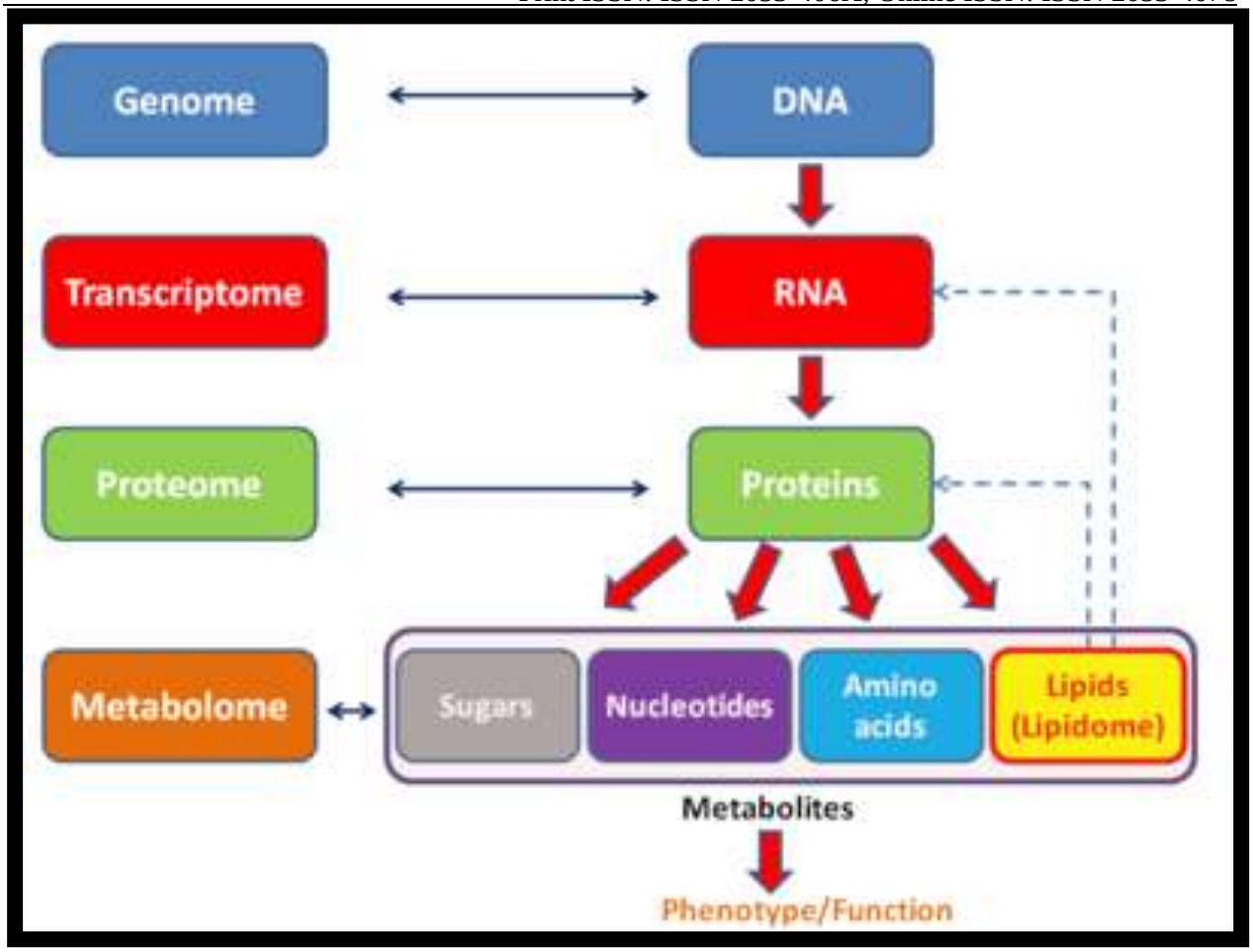


Figure 15: General schema showing the relationships of the **genome,** transcriptome, **proteome**, and **metabolome** (**lipidome**).

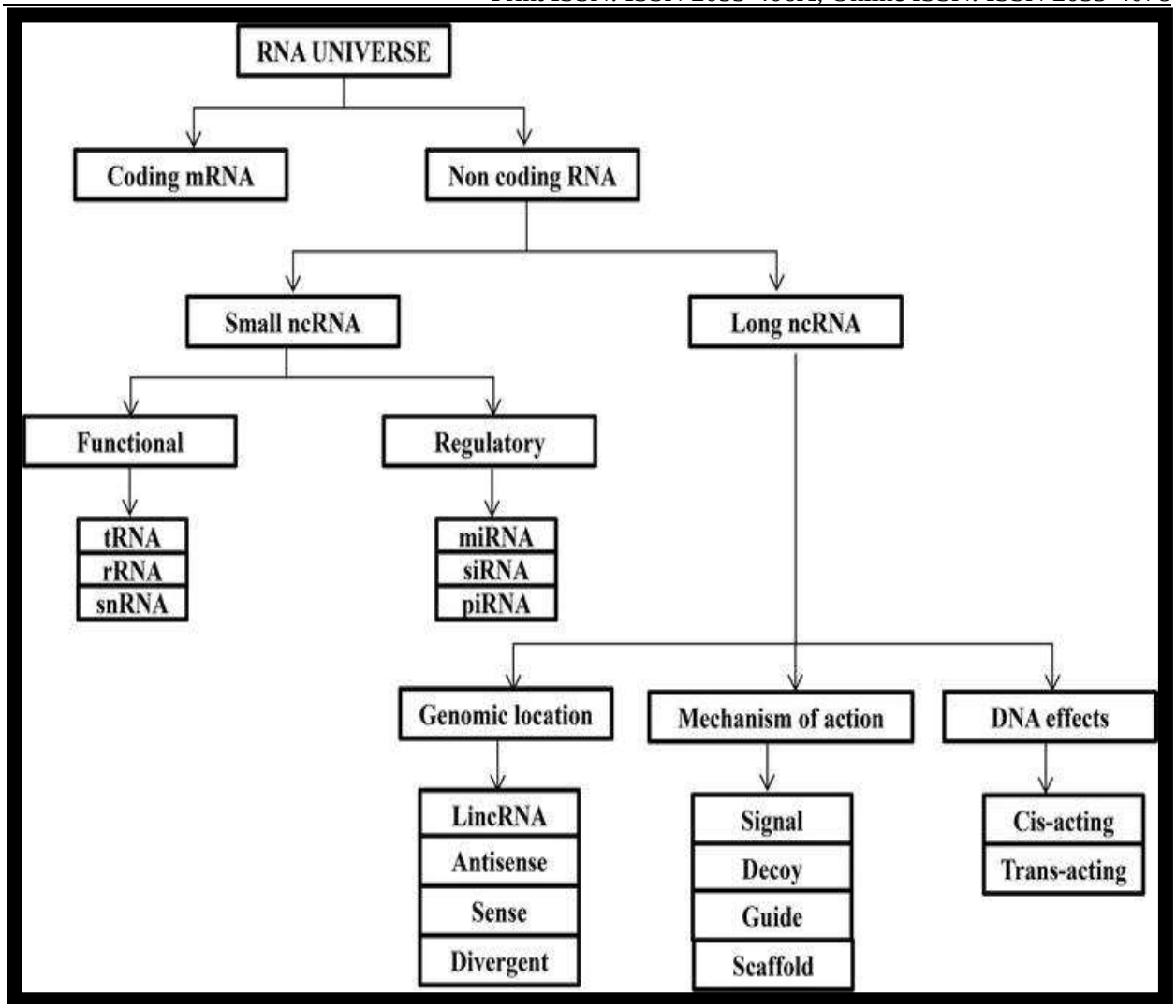


Figure 16. Classification of non-coding RNA (ncRNA).[Srijyothi L et, 2018].

(1)

(2)

(3)

(4)

(5) (6) (7) (8) (9 10 11)


James Watson


Francis Crick


Maurice Wilkins


Rosalind Franklin

(12 13 14 15)

(16)

(17) **(18)**

(19) **(20)**

(21)

Figure 17: Globally disclosed participant scientists emerged, on the worldwide scale, in the course of dynamic and progressive development of both pure & applied biological sciences.

Keys:

(1) Antonie van Leeuwanhoek (1432-1723):

- He was a Dutch business man and scientist.
- He was the first person to discover bacteria in 1674.

(2) Dmitri Iosifovich Ivanovsky (1864-1920):

- He was a Russian botanist.
- He was recognized to be the first discoverer of biological viruses presented in 1892.

(3) Frederick William Twort (1877-1950):

- He was an English bacteriologist.
- He was the original discoverer of bacteriophages in 1915.

(4) Felix d'Herelle (1873-1949):

●He was a French-Canadian microbiologist.

●He was a co-discoverer of bacteriophages in 1917.

(5) Jeaan-Baptiste Lamarck (1744-1829):

●He was a French biologist.

●He was a Professor of "Worms and Insects" in Paris.

●The first scientific theory of evolution he proposed stated that "**acquired characteristics** could be inherited from parents by any offspring". His theory was false, but believed to pave the way for Darwin.

(6) Edward Jenner (1749-1823):

●He was an English physician and scientist who pioneered the concept of vaccines.

●He created the **smallpox vaccine**, the world's first vaccine.

(7) Charles Darwin (1809-1882):

●He was an English biologist (i.e., a naturalist).

●In spite of the fact that he genuinely battled for 40 years, Charles Darwin's theory of evolution which was overartificialized by his diagram of the ape with the human-like face is proved false by **Feleke's Genome Model** of genomic-things at present.

(8) Gregor Mendel (July 20, 1822-January 6, 1884):

●He was an Austrian monk, known as "the father of genetics".

●He was nicknamed as "Man of Science, Man of God" because of his curiosity in studying seven pairs of genetic characteristics on *Pisum sativum* (pea plant) and being a monk in church.

- Gregor Medel's investigation of genetics was a **minute piece of hint** about the secrets of genomic-things. Because of its minuteness Mendel's hint was not enough to disclose the whole miracles of genomic-things and that was the very reason for why scientists were not able to define what a genomic-thing was before the emergence of **Genome Model** of genomic-things.
- The investigation of Gregor Mendel was at the level of individual genes which are the subsets/elements of a Genome and not at the Genome level. The study of genes gives rise to the subject called **Genetics** whereas the study of genomes gives rise to the subject known as **Genomics**.

(9, 10, 11) Matthias Schleiden, Theodor Schwann, Rudolph Virchow (1810-1882):

- Three of them were Germans.
- Three of them were the establishers of Cell Theory. The cell theory is proved false by **Feleke's Genome Model** of genomic-things at present.

(12, 13, 14, 15) James Watson, Francis Crick, Maurice Wilkins, Rosalind Franklin (1916-2004):

- They were the discoverers of DNA model.
- They were English scientists, except James Watson who was American.
- They discovered (saw) DNA molecule but did not know the role or validity of DNA. They were incapable to interpret what they

dicovered or saw. Those who gave them the Nobel Prize did not understand the role of the DNA molecule either.

- Despite the fact that Gregor Mendel's principles were available and had paved the way for them as well as having better technology than Mendel's time, they were passive with the DNA molecule they discovered and somewhat resembled a group of innocent kids that found a stone-like explosive while playing on a roadside without knowing what kind of damage it could do to them!
- Gregor Mendel was able to explain the function of genes (i.e., segments of DNA molecule) without seeing or discovering the DNA molecule itself whereas Watson, Crick, Wilkins and Franklin who saw (discovered) the DNA molecule were unable to explain or interpret the function or role of the DNA molecule.
- Not only these, Gregor Mendel generated his scientific work for human races with his single mind, but Crick & Watson with the team of 4 different minds and then the team of Crick & Watson was given the Nobel Prize whereas no Nobel Prize was given to Gregor Mendel. Now, honoring to Gregor Mendel in recognition of his scientific work for human races; the Nobel Prize must be given to the grand son/daughter descended from the family line of

Gregor Mendel; otherwise, the present scientific community of the world is vulnerable to a serious blame of scientific dishonesty.

(16, 17) A team of scientists in thousands brought together from the globe, being funded with $3 billion US Dollar and involved in the study of Human Genome Project (1990-2003):

- The Human Genome Project forwarded a totteringly wrong and misleading definition for the term **Genome**.
- Its Genome sequencing is not different from what was reported by the discovery of Crick-Watson DNA Model.
- How it was sequencing the Human Genome somewhat resembled driving a car without knowing where to go!!!
- Jumping to conclusion from targetlessly inadequate data and failing of HGP's leaders to understand their own weaknesses could have a negative effect on the achievability of the objective, rendering the participant or competent researchers desperate.

- Funding of $3 billion US Dollar for HGP came from governments of USA, UK Japan, France, Germany and China.

(18) David Haussler (….-20..):

- He is an American Professor of biomolecular engineering and the Director of Genomics Institute in the University of California.
- He has declared that the current Reference Genome Sequence reported by Human

Genome Project (HGP) is still an incomplete sequence and woefully inadequate as a representation of human diversity and genetic variation.

- He has proposed a new Human Pangenome Reference Sequence Project or "Human Pangenome Project" that will be sampled from 350 persons for a far better understanding than from the previous Reference Genome Sequence that was sampled from a single person by HGP.
- David Haussler is better, in his proposed Human Pangenome Project, than Human Genome Project in terms of sample size but his proposal also has lots of unrealized weak points which will be forwarded by the author of this paper in the next article after a few weeks or months.
- At any rate, David's being concerned to achieve a meaningful understanding about the science of human genomics and determination is appreciable and courageously heroic!!!

(19) Dr.Eric Green(during 1990-2003):

- Dr. Eric Green received HGP award for his participation in Human Genome Project as one of the directors.
- The output or achievement of Human Genome Project (HGP) by its leadership was less than expected and below the standard, i.e., below the baseline data [5-7].

(20) Dr. Landers and Dr. Collins (1990-2003):

- Dr. Landers and Dr. Collins were leaders of the Human Genome Project.
- The output or achievement of Human Genome Project by its leadership was less than

expected and below the standard, i.e., below the baseline data.

(21) Feleke Eriso (1962-20..):

- He is an Ethiopian biologist/Immunoparasitologist.
- He generated the dynamic **Genome Model of genomic-things**.
- He proved that **biological viruses are certainly genomic-things**.
- The scientists of the entire world concluded that defining a genomic-thing is impossible, but it is not impossible for the **Genome Model** generated by him!!
- He strongly stated that any **curriculum** of both pure & applied biological sciences designed to educate or train without the knowledge of **Genome Model** would be not teaching but **beating around the bush** and would produce beaters around the bush and not effective & conscious candidates or professionals.
- He stated that no chance is left for any one species of genomic-things to be outside the laws of **Genome Model of genomic-things**.
- In the conclusion section of the **Genome Model** of genomic-things, each of the 20 different conclusive statements is equivalent to a brand new independent article of authentic Nobel Prize standard [28].
- **For the first time,** in the history of progressive development of both pure & applied biological sciences, misleading student children of human races and confusing scientists of biological sciences are wiped out by **Feleke's Genome Model** of genomic-things from the whole system of organisms of the entire world. Applied biological science consists of: (a). Medical sciences, and (b). Agricultural sciences.

- He clearly interpreted and explained **reproductive**, **transformative**, **perpetuative**, and **speciation** functions of **Genome**.
- He is the empowerer of student children of both pure & applied biological sciences to make this planet (Earth) a better place to live for all human races.
- Before the emergence of **Genome Model** of genomic-things, the scientists of the world defined that **biology is the study of living-things** and then they admited that they do not know what a living-thing is!! [29]. Note that the paired term **living-thing** and **nonliving-thing** used herebefore was a wrong & misleading term!!
- He was the first scientist who interpreted & explained the pathogenic cause of **Type 1 Diabetes Mellitus** [4].
- He was the first scientist for correctly explaining by differentiating the pathogen & the host cell in the disease of cancer [8]. He also proved that cancerous genome, diabetogenous genome, and viral genome that enters a human cell are the same in their foreigness to the immune system of a patient and are similarly destroyed by the same immunologically competent cells.
- He was the **revolutionizer** of both pure & applied biological sciences, and **rescuer** of student children of all human races of the world from the **danger of misleading lies** both in pure & applied biological sciences.
- He disproved the **Cell Theory** forwarded by Schleiden, Schwann & Virchow.
- He also totally disproved Charles Darwin's **Theory of Evolution** (**Darwinism**) that was stated as Natural Selection, or Origin of Species (Speciation) of genomic-things.

- Not only that, he directly disproved the concept which stated that biological viruses were nongenomic-things or transitional things between genomic-things and nongenomic-things.
- It is globally and authentically declared that **Gregor Mendel** is the father of **Genetics** because of his contribution of minute hint to biological sciences**.** Now, who is the father of **Genomic-things** & **Role of Genomics** forever?
- **Genome Model** of genomic-things has spectacularly changed the world of biological siences forever; compatible with the **law of conservation of matter**, beginning from individual **elements/atoms** on the periodic table up to the **biomass of a human being**.
- He disproved the concept which dared to state that 95% of human genome is **"junk DNA".**
- He was the magnifier lens of the superscience (the science of genomic-things).
- He is the father of both natural & social scientists as they are genomic-things. In other words, he is the **father of scientists** and the science of genomic-things he deals with.
- He has proved the fact that genome synthesizes genomic-things & their products using**: proteins** (structural & functional) translated from its transcripts, and its **transcripts** directly without translating.
- Biological sciences have been massively developed to the status of **superscience** (the science of genomic-things) by **Feleke's Genome Model** of genomic-things.
- Scientists of biological sciences are authentically called **superscientists** because

biological sciences which are their fields of study have been spectacularly developed to the status of **superscience** [23-28].

- For the **first time**, he interpreted that **genome response** is immunity or immune response against nonself antigens or microbes [24, 27].
- In short, he is the**:**
  - ► father of **Genome Model**,
  - ► father of **genomic-things**, & disprover/disqualifier of the paired erroneous or misleading term called **living-things/nonliving-things**,
  - ► father of **scientists** (of both natural & social scientists for both are genomic-things),
  - ► father of **superscience,** and
  - ► **superpower of mind** in biological sciences forever with no rival or claimer in the entire world. Biological sciences are collectively known as **superscience**.

Biological sciences = pure biology and biotechnology + medical science + agricultural science .

Steps of opening the video: Select, copy and paste the title of the video (only the blue colored & underlined) on Google search space on your computer desktop screen and then press Enter Key of your computer keyboard. Now, click the slide with the correct Title you pasted because when the video is copied & pasted, several other unwanted videos will appear together. When video **1** ends playing, repeat the same steps for playing of video **2**.

Title of video **1:** **□□□ □□□□ ❤ wubete belay || □□□ □□□**
Title of video **2:** **Ayanaw Tirualem - □□□□□ □□□ □ Ethiopia emama □ □□ □□□□□□**

Hereabove in Title of video **1**, did you appreciate how **Feleke Eriso** went back and evaluated/analized the postbirth part of his own **ontogeny**, beginning from the stage of being carried on the back of his mother **Ethiopia** when he was an innocent infant? I hope you will say, **yes!**

Figure 18: The musical film video **1**, is showing how Feleke Eriso was brought up by his mother **Ethiopia** whereas video **2** is displaying genuine feeling of patriotic Ethiopianism.

DISCUSSION

All human races (black, brown, yellow, white) of *Homo sapiens* have the same number of cell types with the same specialized type of **Function** & **Structure** as they have the same **genome** with the same number of **46 DNA** molecules. Distinctive individuality of each of the current 7.8 billion people of the globe is caused by differences in genome sequences brought about by factors such as jumping transposons, point mutations, crossing-over during meiotic cell division and segregation of heterozygote pairs of allelic genes during gamete formation.

The body of a person is not a solid or compact mass. Human body cavities such as buccal cavity, nasal cavities, coelomic body cavity, pelvic cavity, synovial cavities, reproductive cavity, cerebrospinal canal as well as blood vessels, lymphatic vessels & ducts, tubes of the digestive & reproductive tracts including unwebbed separate or isolated fingers and toes are formed by integratedly scaffolding functions & regulations of both coding genes and non-coding various RNAs (i.e., non-coding RNAs are the transcripts of non-coding genes), involving apoptosis which is the programmed death of cells. The number of types of cells, tissues, organs, and organ systems, in all individuals of the current 7.8 billion people of the world is exactly the same because the synthesizer genome in each of them is the same being 46 DNA molecules in size. The task of formation of joints in fingeres & toes, legs & arms, in backbone, and sutures in the skull bone is performed involving the regulatory functions of non-coding RNAs. As differentiation of embryonic stem cells proceeds, for example, in the stem cell committed or determined to be a

skeletal muscle cell, the gene which enhances or promotes the development into the specialized skeletal muscle cell is turned on and others are turned off or silenced by the binding of a Trnscripton Factor on the DNA of the gene to be turned on in the cell committed to become a skeletal muscle cell. The gene is turned on means that the characteristic function of the gene is expressed, leading to the fusion of several myoblast cells, resulting in a specialized multinucleated muscle cell i.e., a fully differentiated & multinucleated skeletal muscle cell. Note that the cell differentiated into the skeletal muscle cell contains all genes which can promote differentiation into lung cell, kidney cell, brain cell, eye cell, bone cell, or into any other human body cell but all of those genes are turned off or silenced and cannot be expressed except the one that promotes the differentiation of the skeletal muscle cell. Thus, in the course of development of these skeletal muscle cells from the embryonic stem cell the synthesis of myosin & actin proteins is enhanced as they are crucially important proteins for contraction & relaxation in skeletal muscles. In all individuals of humans (7.8 billion individuals) the number of types of cells, tissues, organs, organsystems are equal and similar in both structure & function. These differentiated and functionally specialized cells, tissues, organs, and organsystems are functionally interdependent.

For example, if insulin secreting β-cells in pancreas are destroyed by immune response against autointracellular pathogenic genome inside the β-cells, as there will be no insulin for normal glucose metabolism the person will die unless insulin is injected on daily basis. Similarly, if kidneys fail to function or heart stops to perform its task of circulating blood, the individual will die. If testis or ovaries are surgically removed, the individual will be sterile. If the sensitive parts of ear or eyes are completely damaged, the individual person will be deaf or blind because of specialized functional interdependence of body structures in each person of *Homo sapiens*.

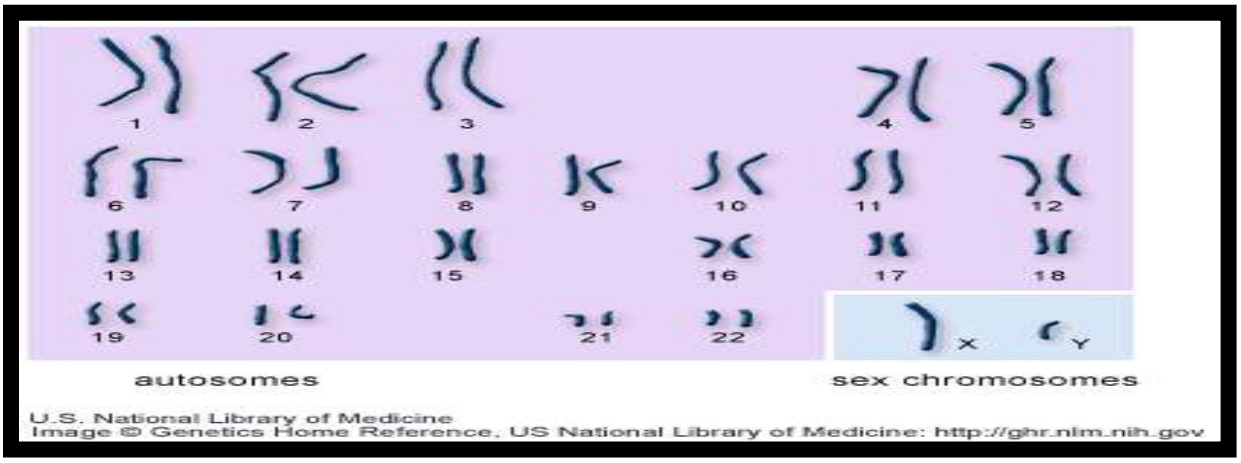


Figure 19: The map of human **Genome** presented by the **Human Genome Project** (Fig. 11)**.**

▪The Human Genome Project (HGP) was not able to sequence all the DNA found in human cells.

▪It sequenced only **euchromatic** regions of the human genome (92.1% of the human genome).

▪The other regions, called **heterochromatic**, are found in **centromers** and **telomeres**, and were not sequenced under the Human Genome Project.

▪The goals of HGP were to:- **identify** all the approximately 20,500 genes in human DNA; **determine** the sequences of the 3 billion chemical base pairs that make up human DNA; **store** this information in databases; **improve** tools for data analysis; **transfer** related technologies to the private sector; and **address** the ethical, legal, and social issues that may arise from the project.

▪It had been stated that though the HGP was finished in 2003, analysis of the data would continue for many years.

The map of human genome must be the map of 46 DNA molecules isolated from the structural proteins (histones & other associated proteins) of human chromosomes. But according to HGP, the human genome or the map of human genome is composed of 46 human chromosomes which is completely wrong (Figs. 11 and 18)!! As each of the 46 chromosomes contains only 1 DNA molecule each of the 46 DNA molecule can be labeled by the identity number of the chromosome that contained it (i.e., DNA1, 2-22) and the last pair of sex DNA molecules can be labeled with x & y (DNA_x, DNA_y). In the study of Human Genome Project, step 1 ought to be isolating the 46 DNA molecules from the structural proteins of the 46 human chromosomes. These isolated 46 DNA molecules represent the human **Genome** and serve as the indispensable **baseline datum**.

Based on this datum, the 23 different homologous pairs of isolated DNA molecules are different in length and they also differ in the number of genes they carry. The genes on different pairs of homologous DNA molecules are different in function. Identifying each of about 20,500 genes, knowing its function, and on which DNA molecule it is found and so on are crucial & of critical importance . Without the baseline datum of isolated DNA molecules it cannot be didactic or impartive for teaching student children of both pure & applied biological sciences and the objectives of HGP cannot be desirably achieved either, but beating around the bush and disguising.

HGP reported that it had completed data collection in 2003 and analysis of data would continue for many years. What HGP reported as data collection was DNA sequencing what had been clearly explained by Crick-Watson DNA-Model many years ago and DNA sequencing alone without isolating DNA molecules from structural proteins of chromosomes was not helpful to achieve the proposed goals of HGP. The set of data collected (DNA sequencing) by HGP was of below standard & irrelevant for its goals and that was the reason for why it had been said that data analysis would continue for many indefinite number of years. From such data collected unconsciously by trial and error no conclusive & no desirable outcome would be achieved!! Hence, Human Genome Project was a program in which time and money ($3 billion US Dollars) were wasted to achieve

no desirable outcome, disguising, pretending or deceiving the nations who funded the project.and to mislead student children of all human races of the world in both pure & applied biological sciences!!!! We cannot lie at the expense of student children of science who will make this planet a better place to live for humans; otherwise, it is a serious academic crime on student children of all human races of the world. In short, how the HGP had been performed was analogous to driving a car without knowing where to go!! In human body, we have so many cells that are functionally & structurally differentiated or specialized into different types of:- cells, tissues, organs, and organsystems. We have muscle cells, nerve cells, eye cells, lymphocytes, bone cells, kidney cells, liver cells, lung cells, heart cells, skin cells, macrophages, ovary cells, testis cells, etc. On which type of cell's genome did HGP conduct **Genome Sequencing?** This is an another exclamatory wonder to what extent we have been attempted to be disguised & misled!! In order to hide the unconscious beating around bush, it was said that for analysis of data even one year could not be enough and should take many years, because stating like that was better/safer for the funded participants than reporting that their approach was unwise and as the result no desirable outcome had been achieved.

The author of this paper would like to inform **Professor David Haussler** to withhold his **"Human Pangenome Project"** soon and discuss with **Dr. Feleke Eriso**, or he would be stacked in a marsh of problem from which he could not come out but be morally cracked.

CONCLUSION

 The science of genomic-things is superior to all branches of natural science because the scientist himself, who creates all other nonbiological sciences, is a genomic-thing and belongs to biological sciences. The scientist should know himself first what he is before creating other nonbiological sciences. We don't have to get into dirty arguments such as producing deadly weapons, being careful not to miss that we need other sciences but the fact that the science of genomic-things is the superscience and it is the science of priority to invest in cannot be denied by any means [23].

 The science of genomic-things is not as simple as digging the moon in space to find precious minerals!! Becareful, going to moon and digging it for minerals is a giant victory in science but when you compare it with the science of genomic-things, it is as simple as anything. **Genome** is a self-reproducing/self-replicating, miraculous, totally self-operating without involving skill or hand of man, absolutely natural being automatic, and self-acting super-machine in its mechanisms of **synthesizing genomic-things** tending to be beyond the comprehension with a human mind!!! The currently existing 7.8 billion people of the world have been synthesized by the **genome** of *Homo sapiens*. The size of *H. sapiens's* genome is

46 DNA molecules. With all these marvelous scientific truths in mind, the science of genomic-things is a **superscience** being the science of priority to invest in [23].

 The **enormous lie** that resided in medical science stated that only 2-5% of human genome is composed of coding genes for proteins and the 95% of it that is noncoding for proteins is **Junk DNA** which means useless being good for nothing. This huge misleading mountain of lie in medical science is irreversibly dismantled and pulverized into dust by **Feleke's Genome Model** of genomic-things!!!!

 In the automatic functional & structural performance of human genome, every component of it is indispensably useful and none of it is **junk DNA** at all!! 100% of a genome's components, in all species of genomic-things from biological viruses up to humans, are unavoidably useful in the task of synthesizing the individuals & populations of its species in different ecosystems on Earth let alone those of human genome!!!!

 The genome synthesizes genomic-things & their products using:

►**proteins** (functional or regulatory such as signalling) translated from its transcripts, and

►its **transcripts** directly without translating [23-28].

 **A crucial message to superscientists of the world:**

Scientists of biological sciences must communicate among themselves and form a team of superscientists to establish a coordinated **Global Center of Superscience** (the best organization out of the bests ever established by humans on Earth) which will be of the highest superiority in validity of making this planet a better place for humans to live. Look, NASA center of space science, advanced military weapons of USA & WHO couldn't protect Americans and others from dying due to COVID-19!! Humans are not able to fully protect themselves from such pandemic diseases and many other disasters (eg., failure in Environmental Protection and the consequences) which are manageable by wisdom of biological sciences, because humans' consciousness about genomic-things until the emergence of **Feleke's Genome Model** has been at the level of **beating around the bush**!!!! If we staple minute hinting pieces of scientific truths/investigated knowledge from different disciplines of biological sciences into applicably dynamic capacities, we will prove that we are spectacularly superscientists; otherwise & if we do not work together, our investigated scientific truths (here and there) of biological sciences will be dissipated!!

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Respected reviewer scientists and readers of this paper! Please open and observe the following 5 different musical films/videos, one by one separately from one another. You observe these musical videos in **Honor of Human Genome(46 DNA molecules)** which has been synthesizing us with its automatic mechanisms since the emergence of *Homo sapiens* & will continue doing the same for an indefinite number of human generations time to come. [Video number **1** is a musical film on **Type 1 diabetes mellitus and pathogenic mutation** and politely requesting global scientists of biological sciences to delete the misleading erroneous terms known as **"living-things" &_"nonliving-things"** from textbooks of biological sciences and replace by the correct ones referred to as **"genomic-things" & "nongenomic-things"_[23, 24]** ; videos **2** & **3** are core musical films in honor of human **Genome** studied in this manuscript; in video **4** appreciate the **Genome** that synthesized the male & female *Walia ibex***;** and in video **5** admire the **Genome** which synthesized the beles plant (*Opuntia ficus-indica*) & then appreciate the number of **food-chains** created by that wonderful plant in the Ecosystem (amazing environmental validity!!!!)]. Not only that, beles is also very strongly protective against soil erosion and look at the type of ground on which it flourishes to yield the abundance of fruits we will,be observing!! You give care neither for the beles plant nor for the ground on which it grows; you go to it only to harvest the fruits it yields.

Steps of opening the video: Select, copy and paste the title of each video (only the blue colored & underlined) on Google search space on your computer desktop screen and then press Enter Key of your computer keyboard. Now, click the slide with the correct Title you pasted because when each of the 5 videos is copied & pasted, several other unwanted videos will appear together. When the play of the video is ended, close it and copy paste the next video.

Title of video **1:** **Ethiopian_music- Alemeye Getachew - Ya Lela Yehe Lela(□□□... □□ □□...) - New Ethiopian Music 2017**

Title of video **2:** **Bereket Mengisteab - New Eritrean Music - Guayla - Nei Telo Remix 2020**

Title of video **3:** **Ethiopian Music - Demere Legesse □□□ □□□ [via torchbrowser.com**

Title of video **4:** **Eri Art - Sami Ezra (Maaro) □□□ - New Eritrean Traditional Music 2020**

Title of video **5:** **New Eritrean Music, Russom G-Giorgis - Belesna Mkrti 2020**

Human Genome is one of the several millions of genomes found in genomic-things of the world. If you were an assigned professional to give a letter grade to the best of your scientific honesty, would you hesitate to give an $\mathbf{A}^{+}$ for the **Genome** of beles plant about its **productivity** & **validity** in its Ecosystem**?** Are you persuaded to believe that the beles plant could be one of the fruit-plants offered to our original parents Adam & Eve to feed on with no human labor or effort?

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References

[1]. Scott GB, Wynter EA, Cook GP. Detecting variable (V), diversity (D) and joining (J) gene segment recombination using a two-color fluorescence system. Mob DNA. 2010; 1: 9.
doi: 10.1186/1759-8753-1-9

[2]. Zelm MC, Burg MV, Ridder D etc. I_g gene rearrengement steps are initiated in early human precursor B cell subsets and correlate with specific transcription factor expression. Journal of Immunology. 2005; 175(9): 5912-5922.
DOI: https://doi.org/10.4049/jimmunol.175.9.5912

[3]. Wacta T, Wallerich S, Becskei A. Stochastic gene choice during cellular differentiation. Documents2. 2018; 24(13): 3503-3512.
https://doi.org/10.1016/celrep2018.08.074Getrightsandcontent

[4]. Serov O, Serova I. Genes and chromosomes: control of development.Anais da Academia Brasileira de Ciencias. 2004; 76(3): 1-10.
https://doi.org/10.1590//50001-37652004000300007

[5]. Collas P, Noer A, Timoskainen S. Programming the genome in embryonic and somatic stem cells. Journal of Cellular and Molecular Medicine. 2007; 11(4): 602-620.

[6]. Kumari P, Sampath K. CncRNAs: Bi-functional RNAs with protein coding and non-coding functions. Semin Cell Development Biology. 2015; 53: 168.
doi: 10.1016/ 1.semcdb.2015.10.024

[7]. Collins LJ, ChenXS. Non-coding RNAs are a group of RNA transcripts that do not necessarily code for protein products, as they make instead potentially functional RNAs. Progress in Molecular Biology and Transcriptional Science. 2018; 1-15.

[8]. Clamp M, Fry B, Kamal M, Xie X, Cuff J, Lin MF, Kellis M, Lindblad-Toh K, Lander ES. Distinguishing protein-coding and noncoding genes in the human genome. PNAS. 2007; 104(49): 19428-19433.
https://doi.org/10.1073/pnas.0709013104

[9]. Stephens PJ, Greenman CD, Fu B, Stratton MR, Futreal PA, Campbel PJ. Massive Genomic Rearrangement Acquired in a Single Catastrophic Event during Cancer Development. Cell Cancer Network. 2011.

[10]. Koltsova AS, Pendina AA, Efmova OA, Chiryaeva OG, Kuznetzova TV, Baranov VS. On the complexity of mechanisms and consequences of chromothripsis: An Update. Front Genet. 2019. https://doi.org/10.3389/fgene.2019.00393

[11]. Kempfer R, Pombo A. Methods for mapping 3D chromosome architecture. Nature Reviews Genetics. 2019.

[12]. Hube F, Frankastel C. Coding and non-coding RNAs, the Frontier has never been so blurred. Front Genet. 2018; 9: 140.

[13]. Surani MA. Genomic Reprogramming: Essentials of Stem Cell Biology. Ed.3, 2014.

[14]. Palazzo AF, Gregory TR. The case for JUNK DNA. PLoS Genet. 2014; 10(5): e1004351.

[15]. Hangauer MJ, Vaughn IW, Mcmanus MT. Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs. PLOS. 2013; https://doi.org/10.1371/journalpgen.1003569

[16]. Palazzo AF, Lee ES. Non-coding RNA: what is functional and what is junk? Front Genet. 2015; https://doi.org/10.3309/fgene.2015.00002

[17]. Lj J, Liu C. Coding or noncoding, the converging concepts of RNAs. Front Genet. 2019; https://doi.org/10.3389/fgene.2019.00496

[18]. Srijyothi L, Ponne S, Prathama T, Ashok C, Baluchamy S.Roles of non-coding RNAs in transcriptional regulation. 2018; DOI: 10.5772/intechopen.76125

[19]. Sampath K, Ephrussi A. CcnRNAs: RNAs with both coding and non-coding roles in development. Development. 2016; 143: 1234-1241. doi: 10.1242/dev.133298

[20]. Chalfant CE, Ciaraldi TP, Watson JE, Nikoulina S, Hennry RR, Cooper DR. Protein kinase CΘ expression is increased upon differentiation of human skeletal muscle cells: dysregulation in type diabetic patients and a possible role for protein kinase CΘ in insulin-stimulated glycogen synthase activity. Endocrinology. 2000; 141(8): 2773-2778.

[21]. Koussoulakou DS, Margaritis LH, Koussoulakos SL. A curriculum vitae of teeth: evolution, generation, regeneration. International Iournal of Biological Sciences. 2009; 5(3): 226-243.

[22]. Sharpe PT, Young CS. Test-teeth. Scientific American. 2005; 293(2): 34-41.

[23]. Feleke E. Genomic-things. International Journal of Development Research. 2020; 10(05): 35498-35504.

[24]. Feleke E. Role of Genome-Model in type 1 diabetes mellitus. European Journal of Biology and Medical Science Research. 2019; 7(3): 35-48.

[25]. Feleke E. Biological viruses are certainly living-things and switching off genomic metabolism. European Journal of Biology and Medical Science Research. 2019; 6(5): 19-41

[26]. Feleke E. Dynamic and detailed Genome-Model of living-things. International Journal of Development Research. 2018; 08(08): 22138-22152.

[27]. Feleke E. Immune responses against autointracellular pathogenic genomes or cancered cells. International Journal of Development Research. 2018; 08(07): 21489-21496.

[28]. Feleke E. Genome-Model of living-things, definition of a living-thing, and the position of biological viruses among living-things. International Journal of Current Research. 2017; 9(07): 53764-53778.

[29]. Toole G and Toole S. Understanding Biology for Advanced Level, London: 1987; 2-3.

Neither any lie nor beating around the bush is allowed to reside in **superscience!!**