**To Which Extent are the Non-Protein Coding Regions of the Genome implicated in Human Genetic Diseases – Contrast Mendelian versus Common Complex Diseases**

**Introduction**

Human beings have a pattern and sequencing of nucleic acid, known as the Human Genome. It is encoded in the form of DNA within 23 pairs of chromosomes, found in cell nuclei, and within individual mitochondria in a mall DNA molecule. These are assessed individually as the mitochondrial genome and nuclear genome. A collaborative research program known as Human Genome Project was conducted to study the architecture and details of human beings' genes. This major outcome of the Human Genome Project was that it helped us explore detailed knowledge about the function, organization, and structure of the complete set of human genes. This knowledge can be regarded as a particular set of data, which is inherited from parents and is required for the proper development, maturation, and function of an individual. According to scientists, the human genome consists of protein-coding and non-coding regions; according to scientists, DNA is made up of 1 percent protein-coding genes and 99 percent noncoding genes (Zhang & Lupski, 2015).

Noncoding DNA is not involved in protein synthesis; it was once referred to as junk DNA and considered to be of no particular importance. With research, it became evident that some part of it is essential for cell functioning, most distinctively regulating gene activity. For instance, noncoding DNA consists of particular sequences that perform the function of regulatory elements, which dictate the on and off function of genes. These regions provide sites for attachment of specialized proteins, such as transcription factors, and regulate the process by which information from genes is converted into proteins (Thomas & Kejariwal, 2004). Multiple types of regulatory elements are present in noncoding DNA, such as Promoters, which are located just in front of the gene and provide binding sites for proteins involved in the process of transcription. Enhancers are another type of regulatory element that has binding sites for proteins that assist in inactivating transcription. Proteins that repress transcription have their binding sites located on silencers. Proteins that control transcription in multiple ways are present on insulators. Some insulators prevent transcription by blocking enhancers. Others repress gene activity by preventing structural changes in the DNA. Moreover, both functions can also be played by some insulators.

Noncoding DNA has certain regions that play a role in the synthesis of multiple types of RNA molecules. Specialized RNA molecules which are produced from noncoding DNA include [ribosomal RNAs](https://medlineplus.gov/images/PX0000HK_PRESENTATION.jpeg) and [transfer RNAs](https://medlineplus.gov/images/PX0000Q4_PRESENTATION.jpeg), which participate in the assembling of amino acids, the building blocks of proteins. Short lengths of RNA called microRNAs halt protein synthesis, and long noncoding RNAs are longer lengths of RNA that play multiple roles in modulating gene activity. Noncoding DNA also contains some structural elements of chromosomes. For example, telomeres are formed by repeated noncoding DNA sequences at the ends of chromosomes. While genetic material is being copied, the ends of chromosomes are protected from degradation by telomeres. Satellite DNA is formed by repetitive sequencing of noncoding DNA, which is a part of other structural elements. The X-shaped chromosome pair has a constriction called the centromere, which satellite DNA forms. Heterochromatin, which is condensed DNA, is crucial for maintaining the chromosome integrity and regulating gene activity, is also formed by satellite DNA (Gloss & Dinger, 2018).

The focus of study had exclusively been on the coding genome in pursuit of disease-causing variants in the past. This particular perspective has been exceptionally fruitful, resulting in recognition of thousands of disease genes, but overlooks the disease relevance of the remaining genome. State-of-the-art technologies, including chromosome conformation capture and ChIP-seq, offer the latest techniques for the noncoding genome's organized appraisal. This information has disclosed noncoding DNA's significance in elemental processes such as 3D chromatin folding and gene regulation. Recent studies in the fundamentals of chromatin folding have unearthed an empirical structure of the human genome, called topologically associated domains that furnish a platform for enhancer-promoter contacts. Mutations in the non-coding genome can disrupt gene regulation by losing function, causing reduced gene expression, or a functional gain causing gene overexpression. Normal chromatin folding is disturbed by structural variations such as duplications, inversions, or deletion. It may cause the disruption or relocation of topological associating domains and the repositioning of enhancer elements with continuous gene misexpression. Multiple studies explain these as basic disease mechanisms in cancer and developmental anomalies. Consequently, the human genome's regulatory framework has undeniable significance when studying the pathology of disease (Hrdlickova, de Almeida, Borek, & Withoff, 2014).

Nucleotide variants associated with diseases recognized in genome-wide association studies (GWAS) are usually not found in coding regions. Rather, the non-coding regions of the genome contain most disease-associated index SNPs. The latest CRISPR/Cas9 genome editing offers new chances to investigate common non-coding types found in cis-regulatory elements. Recent studies have shown that the FTO allele, which demonstrates the strongest genome-based linkage signal for obesity, acts as a function gain. The research found that a common Parkinson disease risk variant, regulating the expression of α-synuclein (SNCA), a key gene involved in the pathogenesis of Parkinson's disease, is present in a non-coding distal enhancer element. Cleft lip with or without cleft palate is another example of a noncoding variant located at locus 8q24. The term position effect describes balanced translocations and other structural rearrangements that cannot be demonstrated by the definition of the variants only (Spataro et al., 2017). An example of this disease mechanism is Liebenberg syndrome, an autosomal dominant disease in which the upper limbs acquire the lower limbs' morphological features. Studies have shown that miRNAs are involved in cancer and cardiovascular, neurodegenerative, and autoimmune diseases. Downregulation or upregulation of the targets results from changes in the number of particular miRNAs, causing deregulation of the pathways involving those targets. In human diseases, this type of deregulation of miRNA levels can occur in multiple ways. Disrupted functions of the enzymes regulating the miRNA biosynthesis pathway have been incriminated in human disease. DiGeorge syndrome, caused by the haploinsufficiency of DGCR8, is a classic example; this autosomal dominant disorder occurs due to deletion of hemizygous chromosome 22q11.2, which produces various phenotypic defects, including autoimmunity immunodeficiency (Zhang & Lupski, 2015).

**Conclusion**

Multiple environmental factors and susceptibility loci interact with each other and result in complex disorders. These are more prevalent in the general population, while Mendelian disorders having predictable inheritance patterns are comparatively rare and result from a single mutation in a gene that causes the disease. Incomplete penetrance and heterogeneity suggest that there is no absolute difference between common complex and Mendelian disorders and that there is a continuum between the two. Advances in research indicate that there are now many catalogs of susceptibility loci that contribute to common complex disorders and mutations resulting in Mendelian hereditary diseases, including those of the Genome-Wide Association Studies (GWAS) and the Online Mendelian Inheritance in Man (OMIM) Catalogue. Mendelian diseases are referred to as monogenic diseases, and complex diseases are referred to as polygenic disorders. Different genetic models are being utilized in studying these diseases. There are multiple genes found in humans that are also known now to occur in other organisms. Researchers can perform analysis on mice in which deletion or mutation of a diseases-associated gene has been carried out, after which a detailed analysis phenotypically of the mutant mice is carried out. It helps a great deal in unraveling the function of the corresponding gene in humans. Distinct inheritance patterns including co-dominant, autosomal dominant, recessive, and X-linked (sex-linked) dominant or recessive help recognize mendelian disorders (Clamp et al., 2007).

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