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Implications of the Human Genome Project in Dentistry – Narrative Review

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KEYWORDS:

Human Genome Project, DNA Sequencing, Genome Sequencing, Gene activity.

ABSTRACT:

Introduction: The Human Genome Project (HGP), one of the largest scientific projects in history, aims to decipher the entire human genome's sequence and comprehend the roles of its numerous components. In 1990, the project formally started as a worldwide cooperative endeavour including scientists from all across the world. The principal objective comprised organizing the entire human genome by mapping and sequencing, pinpointing the sites of particular genes and comprehending their roles.

The HGP was characterized by its large scale institutional approach, scientists, researchers and scholars from various nations, disciplines and institutions. For the project to succeed, this collaborative paradigm was essential as it allowed for the efficient sharing of resources, expertise and data. Nonetheless, there were difficulties and disagreements associated with such a large and intricate project.

The question of data ownership and access was one of the main points of contention around the HGP. The project involved a massive amount of genetic information and questions arose about who had the right to access and control the data. Ethical considerations regarding the use of genetic information also came to the forefront, prompting discussions about privacy, consent and the potential misuse of genetic data. Despite the challenges the HGP achieved significant milestones. The first outline of the human genome sequence was finished in 2001, offering a thorough overview of the genetic blueprint that constitutes an individual human. This breakthrough laid the foundation for numerous advancements in genetics and medicine.

The development of the Human Genome Project and its implications on numerous fields are briefly discussed in this article including Dentistry its role in understanding the genetic basis of diseases and exploring human evolution its contribution in understanding the similarities and differences between human and other species, illuminating the evolutionary mechanisms that have moulded the diversity of life.

1. Introduction

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Key words: Human Genome Project, DNA Sequencing, Genome Sequencing, Gene activity.

Introduction: The genome, or gene, is an organism's unique compilation of deoxyribonucleic acid (DNA), the chemical compound that holds the genetic instructions required for all organisms to develop and function. DNA molecules are made up of a pair of helical strands. Nucleotide bases are the four basic building blocks that make up each strand. Approximately 3 billion of these base pairs are found in the entire human genome which are present in the 23 pairs of chromosomes that are found in the nuclei of all of our cells. There are hundreds to thousands of genes on each chromosome that carry the instructions needed to make proteins. The human genome is expected to include 30,000 genes, each of which produces three proteins on average (Ascencio-Carbajal, T et al., 2021). Genetics has undergone a revolutionary change with the advent of numerous molecular methods for examining genes and gene expressions. The possibility of determining the entire genome sequence has been established by scientists due to these tools. The first complete genome sequenced was the circular genome of human mitochondria in 1981. It was known at that time that the nuclear genome is 2000 times larger than the mitochondrial genome (Flynn S. 2019). However, the major advances in automating DNA Sequencing of large genomes a real possibility in mid-1980 (Hanna, K. E et al 1993).

Sequence Components: The DNA in cellular genomes can be divided into unique sequence DNA, represented only once or in few copies: and various classes of repetitive DNA. The term "unique sequences," sometimes known as "single copy sequences," refers to sequences that exist in the genome as single copies (Davies, J. L et al., 1994). Not all unique sequence material contains protein coding sequences. In humans, unique sequences are estimated to make up roughly 65% of the genome. The percentage of unique sequence DNA contributes to genome complexity. The entire amount of unique sequence DNA is referred to as genome complexity, and it can be expressed in physical units (base pairs) or as a percentage of the genome's overall size. The repetitive sequence DNA are moderately repetitive and highly repetitive DNA Sequences (Donnelly, A et al., 1994). They appear many a time within the genome. The repeated DNA sequences may be tandemly arranged or inter spread within unique sequence DNA in the genome (Hamer, D. H., et al 1993).

What is sequencing?

A DNA segment's base pair order can be precisely ascertained through sequencing. Approximately 50,000,000 and 30,000,000 base pairs constitute every single human chromosome. The bases exist in pairs, and scientists are not required to report both bases in a pair because the identity of one base in a pair dictates the identity of the other members of the pair (Brunner, H. G et al., 1993; Balthazar, J et al., 2023).

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Genome Sequencing

The most important tool in human genome mapping is DNA Sequencing. This refers to the order of bases along the DNA Strand. Due to scheduling and financial constraints, the previous chemical and enzymatic sequencing techniques are not applicable for large-scale sequencing (Collins F. S. 1992). Automated sequencing techniques have been developed that are quicker than traditional approaches (Collins, F., & Galas, D. 1993). The Human Genome Project gave rise to comprehensive microarray technologies that have become today a standard tool in academic and pharmaceutical research institutes for tracking gene activity (Culliton B. J. 1985).

Whole Genome Sequencing

A complete genome sequencing project is necessary to comprehend the role of non-coding DNA and the regulation and function of genes. Because sequencers are limited to processing small DNA segments, sequencing the entire genome at once is not feasible. As a result, the genome is broken up into fragments, which are then sequenced and put back together in the right order to create the sequence for the entire genome (Callier, S. L., et al 2016; Durfy S. J. 1993). There are two methods for sequencing the entire genome that make use of these ideas.

- Shot gun Sequencing.
- Clone by clone approach.

The DNA sequence of an organism's genome can be ascertained by a commonly used laboratory method called shotgun sequencing. There are a number of crucial steps in the procedure.

- **DNA Extraction:** First, the genomic DNA is extracted from the organism's cells. This DNA contains all the genetic information of the organism.
- **• Fragmentation: After being extracted, the DNA is subsequently divided into tiny pieces at random. Although the length of these fragments varies, they usually range from 1000 to 2000 base pairs.**
- **Sequencing:** Each of these fragments is sequenced individually using various sequencing technologies, such as Sanger sequencing or next-generation sequencing (NGS) techniques like illumine sequencing. During sequencing, the bases (adenine, guanine, cytosine, and thymine) in each fragment are determined (Wilson D. J. 1993).
- **Overlap Detection:** Once all the fragments are sequenced, a computer program analyses the sequences and looks for overlapping regions among the fragments. Overlapping sequences are essential for reassembling the genome accurately.
- **Assembly:** Using the detected overlaps, the computer program assembles the fragments back into their correct order, reconstructing the entire genome sequence.
- **Quality Checking:** After the assembly, the resulting genome sequence is checked and refined for accuracy. The sequence is examined for mistakes and gaps, and if attainable, they are fixed.
- **Annotation:** Finally, the annotated genome sequence is analysed to identify genes, regulatory elements, and other important features. Evolutionary biology, genomics, genetics, and other relevant sciences can benefit greatly from the insights provided by this annotated genome data (Jenkins J. F. 2019).

Clone by clone approach involves the following steps:

- Chromosome Mapping: Chromosomes are mapped to understand the structure and order of genes.
- DNA Fragmentation: The mapped DNA is broken down into fragments of a specific size (150 kilobases long in this case).
- Insertion into BACs: Fragments are inserted into Bacterial artificial chromosome (BACs) and then introduced into bacterial cells. Each time the bacteria divide, the inserted DNA fragments also divide and produce identical copies creating bacterial clones (Murray, J. C et al 1994).
- Fragmentation of Bacterial Clone DNA: Individual Bacteria clone DNA is fragmented into smaller DNA sequence. Sequencing starts from the known vector sequence and continues into the unknown DNA sequences.
- Overlap identification: After sequencing, overlapping areas between the fragments are identified by comparing their sequences.

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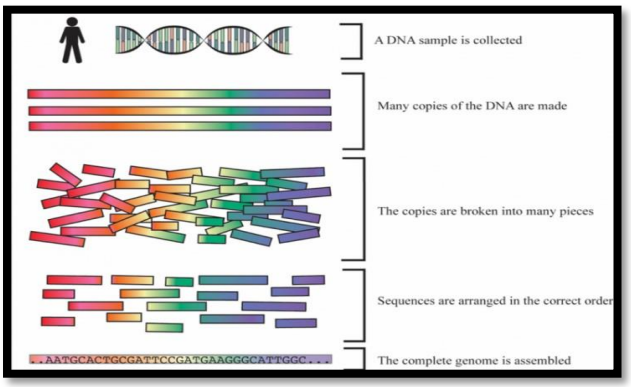

FIGURE 1 WHOLE GENOME SEQUENCING

- Fragment Joining: Overlapping sequences are used to join the fragments, reconstructing the larger fragments initially present in BACs.
- Assembly: The bigger components are put together into chromosomes in accordance with the genome map, which recreates the genome sequence in its entirety.

This method allowed scientists to sequence large genomes by breaking the process into manageable fragments sequencing them individually and then reconstructing the complete genome based on overlaps and mapping information.

Discussion:

The whole human genome's completion provides

- A unique opportunity to understand the role of genetic factors in health and disease.
- Aids in the discovery of genes implicated in the pathogenesis of disease

History of HGP: In the year 1901William Bateson, the biologist coined the word “Genetic” Albert Levan and JO Hin Tjio did not discover the whole number of chromosomes until 1956. Twenty years afterward, the first human gene-globin was successfully cloned. The discovery of the chromosomal count by Jo Hin Tjio and Albert Levan in 1956 marked the beginning of modern genetics. Twenty years afterward, the first human gene—globin—was
successfully cloned. In 1980, David Bostein, Ray White, Mark Skolnick, and Ron Davis demonstrated how restriction fragment length polymorphisms (RFLPs) could be used to identify the genes responsible for human diseases, which marked the beginning of modern genetics. The mid-1980s saw the beginning of the desire to sequence the entire human genome. In reality, during a scientific symposium held in 1984–1986 under the auspices of the US Department of Energy and other organizations, the notion of sequencing the entire human genome was initially introduced. In the US, the Department of Energy and the National Institute of Health collaborated to develop this programme.

Dr. James D. Watson was recruited to lead the Human Genome Research office in 1988. Watson and Francis Crick shared the Nobel Prize for discovering the structure of DNA. This office later expanded to become the National Human Genome Research Institute. The Human Genome Project began in the late 1990s and involved the establishment of genomic centres in six nations: the United States, the United Kingdom, Japan, France, Germany, and China.

A "rough draught" of the genome was completed in 2000 and jointly announced by British Prime Minister Tony Blair and then-US President Bill Clinton on June 26, 2000. This was made possible by extensive international cooperation, advancements in the field of genomics (particularly in sequence analysis), and significant advancements in computing technology. Five years ahead of schedule and thanks to ongoing sequencing, the genome was declared nearly complete in April 2003. The publication of the final chromosome's sequence in the journal "Nature" in May 2006 marked yet another significant milestone towards the project's completion.

Goals of HGP:

The HGP was launched with the following goals:

To determine the identities of all 20,000–25,000 genes found in human DNA.

• To ascertain the 3 billion chemical base pair sequences that comprise human DNA.

• To keep this data in databases.

• To enhance data analysis tools.

• To give the private sector access to relevant technologies.

• To handle any potential ELSI (ethical, legal, and social issues) arising from the project (Meslin, E. M et al., 1997; Meagher, K. M., & Lee, L. M. 2016).

Results of HGP:

The results of the draft sequence released by HGP:

- The genome has a total size of 3.2 Gb. Different types of repetitive sequences make up a large portion of DNA. The chromosomes' peri centric and subtelomeric

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regions have significant recent segmental duplication from other parts of the genome.

- It is estimated that there are roughly 32,000 coding genes in the genome. In human DNA, introns are longer and the gene density is higher in GC-rich areas.
- Only 94 protein families out of 1278 are unique to vertebrates. The complexity of the proteins that our genes encode sets us apart from other non-vertebrate species.
- Male mutation rates are twice that of female mutation rates.
- Over 1.4 million SNPs are dispersed over the entire genome. SNP stands for "single nucleotide polymorphisms. “A polymorphism brought about by one nucleotide alteration. SNPs are thought to be responsible for the majority of genetic differences found in human individuals. They are helpful in locating the genomic locations associated with disease and the unique drug-reaction variants.

Potential Benefits of Human Genome Project

There are most likely between 30,000 and 40,000 human genes, according to the HGP. They can now be located by the finished human sequence. The final result of the HGP has provided the world with a wealth of comprehensive knowledge regarding the composition, arrangement, and operation of the whole set of human genes (Peters, K. F. et al 1994). Because of the sequence, a comprehensive catalogue of all the components of the genome and the ways in which proteins interact with one another to build pathways and networks can now be developed. This will facilitate the development of more advanced approaches to disease diagnostics, early identification of genetic susceptibility to illness, medicine development, and gene therapy. Comprehending the human genome will be helpful in evaluating the hazards associated with radiation, chemicals, and toxins as well as identifying genetic variations that predispose some individuals more than others (Zneimer S. M. 2002). The DNA Sequencing techniques also enable the detection of potential suspects, victims of crime and also resolves paternity disputes (Walker, R. L., & Morrissey, C. 2014). HGP will also unravel complicated biological processes including development, differentiation and coordination of cellular activities (Shipp, A. C., & Patterson, A. P. 2003).

HGP is still incomplete!

The highly repetitive areas of the centromere and telomere of the chromosome cannot be sequenced with the technology currently used to sequence the human genome (Simmons K. 1985). The centromeres are millions, if not tens of millions, of base pairs long, and they are mostly completely unfinished. In addition, the telomeres exhibit significant levels of repetition, with the majority of the 46 chromosomal ends being inadequately completed. Until new technology is developed that allows us to sequence them, it is likely that the telomeres and centromeres will remain undiscovered. Apart from these areas, the genome still has a few hundred gaps that need to be filled. Genes are unlikely to be present in the majority of the residual DNA, which is extremely repetitive.

HGP Implications in Dentistry

Human genetics and the use of novel molecular-based diagnostic and therapeutic technologies will become increasingly important to dentists. The Human Genome Project has made it possible to develop new technologies that are critical to comprehending the various anomalies associated with disorders of the oral cavity (Getting, E., & Hart, T. C. 2003). The intersection of the human genome, information technology, and biotechnology—miniaturizations and nanotechnology—marks the future of oral health education and proposes new professional competences for the field of oral health in the twenty-first century.

Unravelling the human genomic sequence now allows accurate diagnosis of numerous craniofacial and or facial conditions. One important aspect in the genomic research is the comparative genomic analysis. The HGP has developed unique tools that allow the sequences of various organisms to be quickly analysed for commonalities. The LAST tool can be used, for instance, to compare the genomes of two distinct microbes that cause dental caries. Proteomics, bioinformatics, comparative and microbial genomics, human genome data, and other relevant technologies will all be further integrated to create the basis for proactive prevention and intervention as well as innovative and more effective treatment options. Through the genomic approach it is clear that genetics is becoming integrated into health care in all medical specialties, including Dentistry. It is now easy in the post genomic era for a dentist to access the

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information of the human genome and study any particular gene of interest in any pathological conditions It is evident from the genomic method that genetics is increasingly being included into dental care, among other medical specializations. In the post genomic era, a dentist can now easily access human genome information and research any specific gene of interest in any clinical condition.

In summary, the Human Genome Project has had a significant influence on the development of genetics and has left a long-lasting legacy. The Human Genome Project (HGP) has set the stage for a new era of genomics research with its lofty goals, collaborative methodology, and ground-breaking discoveries. The insights learned from the HGP are carried forward by other large-scale genomics initiatives, which further our investigation of the complex genetic landscape that defines human biology.

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