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Mitochondrial Genetics and Human Disease: A Comprehensive Review from Genetic Principles to Systems Biology Perspectives: A Narrative Review

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ABSTRACT

Objective: *Mitochondrial diseases are a category of clinically diverse and difficult to diagnose disorders that are also challenging to treat. These disorders are caused by mutations of the mitochondrial DNA (mtDNA) or the nuclear DNA (nDNA), which encode mitochondrial and nuclear genes respectively. It is a complicated process in which these two genomes interact with some special genetic characteristics that determine the spectrum of clinical manifestations: the phenomenon of maternal inheritance, heteroplasmy, genetic bottleneck, makes the task of diagnosis a daunting endeavor. This review attempts to uncover the basic genetic concepts of the mitochondrial genome and the revolutionary role of bioinformatics and systems biology in the knowledge of mitochondrial pathology.* ***Method:*** *We explore the concept of the next-generation sequencing (NGS) technologies that have transformed the genetic diagnostics process, allowing to identify causative mutations fast. In addition, we discuss how multi-omics integration and computational modeling could be used to understand the complexity of molecular networks and pathways that are impaired in these diseases.* ***Results:*** *We demonstrate, using case study of particular mitochondrial diseases such as Leigh syndrome, Leber hereditary optic neuropathy (LHON) and mitochondrial cardiomyopathy, how such sophisticated methods are not only enhancing the accuracy of diagnosis but also leading to new treatment interventions.* ***Novelty:*** *Lastly, we explain the recent problems and perspectives of the field, with the prospects of a new era of personalized medicine to patients with mitochondrial disorders.*

INTRODUCTION

Mitochondria, or sometimes known as the powerhouses of the cell, is an important organelle within eukaryotic cells that produces most of the cellular energy as adenosine triphosphate (ATP) through a process known as oxidative phosphorylation (OXPHOS) [1]. Their contribution is however much more than energy production being involved in the vast span of key cellular functions, such as calcium homeostasis, cellular signaling, and programmed cell death (apoptosis) [2]. Although they are significantly important, their dysfunction that results in what are generally referred to as mitochondrial diseases is a major complication in contemporary medicine. Such disorders are notorious to be complicated especially because of their distinct genetic basis.

The only human genetic diseases that are under dual genetic regulation subjected to the control of both small and maternally inherited mitochondrial genome, (mtDNA) and the enormous nuclear genome, (nDNA) are mitochondrial diseases [3]. Only 13 proteins and their RNA machinery required to translate and encode them are encoded by the mtDNA which is a circular molecule and all are core subunits of the OXPHOS

system. By comparison, the nDNA encodes the enormous proportion of the predicted 1,500 mitochondrion protein counts, which are crucial in both mitochondrial biogenesis and mitochondrial homeostasis as well as regulating metabolic processes [4]. Combined with other distinctive properties such as maternal inheritance and the so-called heteroplasmy (presence of mutant and wild-type molecules of the mitochondrial genome within a single cell), this genetic control results in tremendous genetic and clinical heterogeneity [5]. This complication usually turns the process of diagnosing and treating mitochondrial diseases as a long and tedious process to patients and their families [6].

Bioinformatics and systems biology have become the new revolution that can be used to deal with this complexity. They are used in place of the identification of a small number of causative genes in that, these methodologies enable researchers to examine large quantities of biological data (multi-omics) to comprehend the complex networks and pathways that are disturbed in disease [7]. This constitutes a paradigm shift in which one asks what the causative gene is. to How is this genetic defect disease-causing on a systemic level? This review will identify the ways in which the study of bioinformatics and systems biology has allowed scientists to decipher the mysteries of mitochondrial diseases, both to enhance the reliability of genetic diagnosis, as well as to reveal previously unnoticed pathogenic processes, and to open new possibilities to create personalized treatment. Case studies on selected diseases will be provided, the present challenges will be discussed, and the future will be pointed out that will declare a new era in mitochondrial medicine.

RESEARCH METHOD

Mitochondrial Genome and Genetic Principles

The distinctive feature of the diseases caused by mitochondrial abnormalities is the complex genetic basis. Unlike the majority of genetic disorders caused by mutations in the nuclear genome, mitochondrial diseases can result from abnormalities in either of two genomes: the mitochondrial DNA genome (mtDNA) and the nuclear DNA genome (nDNA). This model of dual-genome regulation is the main framework for understanding the genetics of mitochondrial diseases.

A. Structure of the Mitochondrial Genome

The mtDNA is a small, circular, double-stranded DNA molecule, typically 16.6 kb in size in humans, that resides within the mitochondrial matrix. It has two strands, resulting in a heavy strand (H-strand) and a light strand (L-strand). The mitochondrial genome is relatively small compared to the 3.3 billion base pair nuclear genome. It contains 37 genes that encode 13 essential protein subunits of the oxidative phosphorylation (OXPHOS) system, 22 transfer RNAs (tRNAs), and 2 ribosomal RNAs (rRNAs) required for the synthesis of these proteins [8] .The mitochondrial DNA contains a large non-coding region which is called the D-Loop (Displacement Loop). The D-loop is a triple-stranded region and has a role of acting as a promoter for the heavy and light strand and contains necessary transcription and replication elements [9].

The nDNA, on the other hand, encodes the vast majority of mitochondrial proteins, estimated to be over 1,500, which are synthesized in the cytoplasm and then imported into the mitochondria. These nuclear-encoded proteins are crucial for a wide range of mitochondrial functions, including mtDNA replication and maintenance, protein import and assembly, and the regulation of mitochondrial metabolism [10]. This dual genome system allows pathogenic mutations to occur in either genome and follow various modes of inheritance. Nuclear DNA mutations follow Mendelian inheritance models such as autosomal recessive, autosomal dominant, and X-linked inheritance. Mitochondrial DNA mutations have their own mode of inheritance called maternal inheritance.

B. Maternal Inheritance and the Genetic Bottleneck

It is well established that mitochondrial DNA is inherited almost exclusively through the maternal line. The reason for the dominance of maternal inheritance is that the number of mitochondria in an oocyte is large (100,000-200,000), whereas the number of mitochondria in sperm cells is small (100-1,500), and the paternal mitochondria are destroyed after fertilization [11]. A maternal mtDNA mutation is thus inherited by all children, but only the daughters will pass the mutation on to their children. The pattern of mtDNA inheritance was first established in the landmark study by Giles et al. (1980) [12]. Although the general consensus is that mtDNA is inherited exclusively from the mother, there are some rare and contentious reports of paternal or biparental mtDNA inheritance in humans [13].

The other process that is quite noticeable leading to variable expressivity among siblings sharing a common mtDNA and the reason why a heteroplasmic female without symptoms can have affected offspring is called the mitochondrial genetic bottleneck phenomenon [14]. This genetic bottleneck can hardly be inherited by any other way except through the female line, and it is uncertain that any pregnancy would be carried out because of varying degrees of mutated mitochondrial DNA [15]. This bottleneck hypothesis relies on the observation of intergenerational fluctuations in the heteroplasmy of the mitochondrial DNA as well as, it is believed to take place in the ovary during oocyte development probably as a result of significant decrease in the copy number of mitochondrial DNA in primordial germ cells, and subsequent segregation of the mitochondrial DNA in developed oocytes [16].

RESULTS AND DISCUSSION

Heteroplasmy and the Threshold Effect

The other important aspect of the mitochondrial genetics is the problem of heteroplasmy. Hundreds to thousands of copies of the mitochondrial DNA are found in each cell. Heteroplasmy is a condition of a hybrid combination of mutated and wild-type molecules of mitochondrial DNA in one cell or tissue [5]. Mutated mtDNA may be quite heterogeneous in its proportion across tissues and even within cells of a tissue. This heterogeneity is a significant cause of clinical heterogeneity of mitochondrial diseases. The clinical symptoms of the mitochondrial disease usually appear only when the proportion of the mutated mtDNA reaches a specific critical level. This is also referred to

as threshold effect [5]. This level of threshold also depends on the particular mutation and the energy needs of the tissue. Tissues with high energy demands, such as the brain, heart, and skeletal muscle, are more susceptible to mitochondrial dysfunction and generally have a lower threshold for disease expression. The threshold typically ranges from 60% to 90% mutant mtDNA. This explains why individuals within the same family who carry the same mtDNA mutation can have vastly different clinical presentations, ranging from asymptomatic to severely affected [17].

Inherited Mitochondrial Disorders and Clinical Diversity

Mitochondrial disorders (MDs) take place when mitochondria fail to provide the cell with the necessary energy for the normal functioning of the body. MDs may be primary or secondary. Primary MDs arise from mutations that directly affect OXPHOS or the mechanisms necessary for its functioning or mitochondrial biogenesis. Secondary MDs arise from defects in fatty acid oxidation, Krebs cycle, metabolism, or calcium regulation [18]. Overall, 413 genes have been linked to primary mitochondrial disorders (PMDs). mtDNA-related PMDs are estimated to have a prevalence of 1 in 5000 cases, whereas nDNA-related PMDs are rarer, with an estimated prevalence of 1 in 35,000. These mutations may be inherited or occur spontaneously [19]. Notably, there are other factors that contribute to the expression of mtDNA mutation, involving gender, mtDNA polymorphisms, nuclear genetic background, and additional mtDNA mutations, as well as environmental factors such as smoke and drugs [20] (Figure 1).

The combination of dual genomic control, maternal inheritance, and heteroplasmy results in a significant amount of clinical heterogeneity in mitochondrial diseases. The conditions can affect any organ at any time but often have a predilection for tissues with high energy demands. The clinical spectrum of mitochondrial diseases varies from organ-specific disease, as in Leber's hereditary optic neuropathy (LHON), to multisystem disease, as in Leigh syndrome. Several common mitochondrial disorders (MDs) include Leigh syndrome, Leber hereditary optic neuropathy (LHON), myoclonic epilepsy with ragged red fibers (MERRF), and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) [21]. The similarities between the symptoms and other neurological and muscular disorders tend to complicate the clinical diagnosis, which results in lengthy and frustrating diagnostic journeys of patients and their families [6].

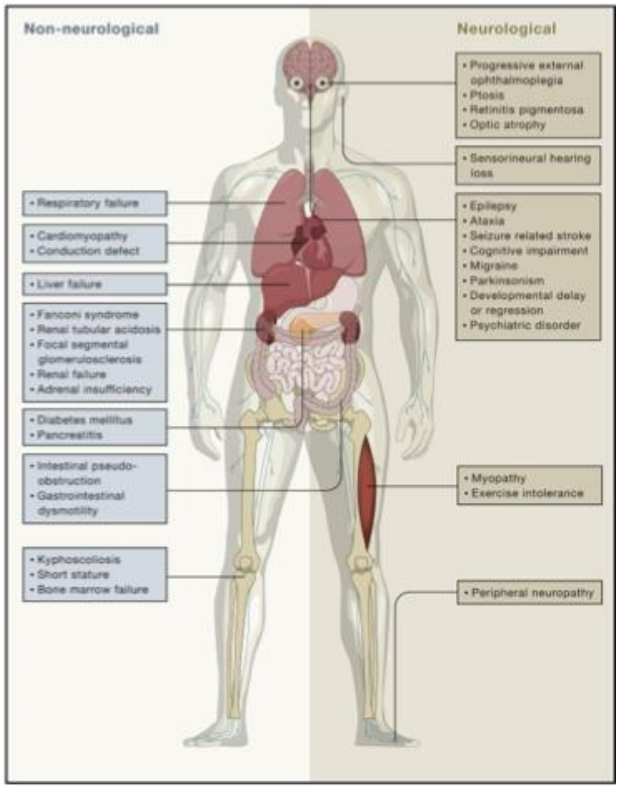

Figure 1. Clinical Features of Mitochondrial Disease. Mitochondrial dysfunction can cause a range of neurological and non-neurological symptoms. The spectrum of tissues involved varies between the mutation (mtDNA or nDNA), heteroplasmy, and age of onset and thus makes it difficult to predict disease progression [6].

The Role of Bioinformatics in Unraveling the Complexity of Mitochondrial Diseases

The introduction of bioinformatics has brought a paradigm shift in the practice of mitochondrial medicine, where less diagnostic by way of invasive biochemical tests was used to diagnose such complex disorders at the initial stage of a diagnosis process, the introduction of a genetics-first method of diagnosis has transformed the practice of mitochondrial medicine [17]. Researchers and clinicians have used bioinformatics tools and methods to analyze the huge volumes of genomic data produced by next-generation sequencing (NGS) methods, resulting in the identification of new disease-causing mutations and increasing the comprehension of the genetic landscape of mitochondrial diseases.

A. Next-Generation Sequencing (NGS) in Mitochondrial Disease Diagnosis

The NGS technologies have played a game changer in the diagnosis of the mitochondrial diseases. Compared to sequencing a single gene at a time, NGS can be used to analyze hundreds or even thousands of genes simultaneously and can significantly increase the diagnostic yield and shorten time to diagnosis. Whole-Exome-Sequencing (WES), Whole-Genome-Sequencing (WGS), and Targeted Gene Panels are considered to be the primary NGS methods in the diagnosis of mitochondrial diseases. WES aims at sequencing every protein-coding part (exons) of the genome. It has played a key role in increasing the level of diagnostic rates of mitochondrial diseases to more

than 50% in certain cohorts as compared to approximately 11% using the conventional methods [17]. WES has also played essential roles in finding over 300 nuclear genes that are connected with mitochondrial disease [18]. WGS offers a deeper insight, as the entire genome (non-coding regions are also sequenced) is provided. This enables the identification of mutations in regulatory regions, profound intronic mutations that can influence the splicing process, and structural variants that are often overlooked in WES [22]. Targeted Gene Panels Targeted gene panels are based on a curated list of genes of known relevance to mitochondrial diseases, including the MitoExome, covering all the genes in the MitoCarta database [17]. first-tier A cost-effective, targeted panel-based test can be used, though it can fail to detect novel or atypical genes of disease.

Although these technologies have shown promise, the analysis of mtDNA data generated by next-generation sequencing (NGS) has its unique set of challenges. The first of these is the presence of nuclear mitochondrial sequences (NUMTs), where mitochondrial DNA has been inserted into the nuclear genome. NUMTs can interfere with the accurate alignment and variant calling of mtDNA, leading to false-positive results. Therefore, specialized bioinformatics pipelines, such as MitoSeek and mtDNA-Server 2, have been developed to distinguish between authentic mtDNA and NUMTs and to accurately estimate heteroplasmy levels [23], [24]. Figure 2 presents a comparative summary of these approaches.

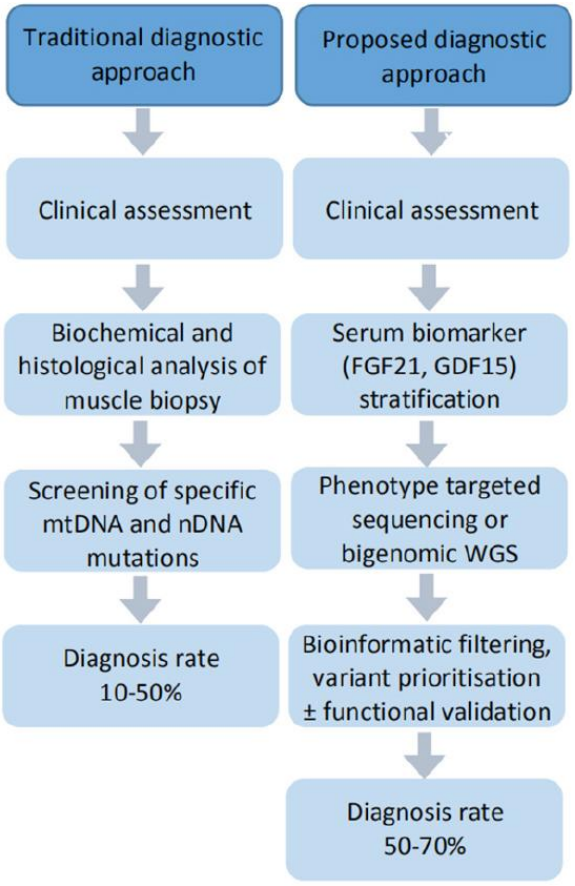

Figure 2. Comparative summary of traditional and proposed diagnostic approaches to mitochondrial diseases [25].

B. Specialized Databases and Tools

The interpretation of the vast number of genetic variants generated by NGS would not be possible without specialized databases and bioinformatics tools. In the field of mitochondrial diseases, several key resources are widely used. MITOMAP is the most authoritative and widely used resource for human mitochondrial DNA variation and its association with disease. It provides a curated list of mtDNA variants and their pathogenicity, supported by evidence from the scientific literature [17]. HmtDB and MSeqDR provide complementary information, such as allele frequencies in different populations and predictions of the functional impact of variants, which helps to place newly identified variants in the correct context [17]. MitoWizz and mtDNA-Server are specialized analysis tools that streamline the process of analyzing mtDNA sequences, from variant calling and annotation to heteroplasmy estimation, saving researchers significant time and effort [24], [26].

C. Pathogenicity Prediction of Variants of Uncertain Significance (VUS(

One of the main challenges in clinical genetics is the interpretation of variants of uncertain significance (VUS), as these variants do not yet show clinical relevance. Conventional predictors of pathogenicity, like SIFT and PolyPhen-2, though originally designed to be used for nuclear DNA, show low prediction accuracy when used for mitochondrial DNA (mtDNA) variants, mainly due to specific evolutionary and biological peculiarities of mitochondrial DNA [17]. To circumvent this limitation, new predictors of pathogenicity, especially designed for mtDNA, have recently been developed. Some of these predictors, like their predecessors, use machine learning approaches to combine different parameters, like evolutionary conservation in different species, protein structure, and population data, to improve prediction accuracy. Some of these predictors include APOGEE and MitoTIP. The former, being a machine learning-based predictor, has shown better prediction accuracy than its predecessors in predicting missense mtDNA variants. The latest version, named APOGEE2, promises even better prediction accuracy by using a better training dataset and modeling framework [27], [28]. The latter, named MitoTIP, is a predictor of pathogenicity of variants in mitochondrial tRNA genes, as these play a significant role in mitochondrial diseases [29]. The development of these predictors has helped in reducing VUS cases, enabling better clinical decisions regarding newly discovered variants.

Systems Biology: Towards an Integrated Understanding of Pathogenic Mechanisms

Whereas bioinformatics focuses on the identification and interpretation of genetic variants, systems biology has made significant progress in understanding the interactions of genetic variants in complex biological networks that lead to the disease phenotype. This is particularly critical in the case of mitochondrial diseases, which have a wide phenotypic spectrum that cannot be explained by the deficit in energy production.

A. From Single-Omics to Multi-Omics Integration

Each "-omics" technology, such as genomics (the study of genes), transcriptomics (the study of gene expression), proteomics (the study of proteins), and metabolomics (the study of metabolites), provides a snapshot of only one layer of the biological system.

Analyzing any of these layers in isolation provides an incomplete picture. The power of systems biology lies in the integration of these multi-omics datasets to build a more comprehensive model of the causal relationships between genotype, protein function, and disease [7]. For example, whole-exome sequencing (WES) may not reveal any causative coding variants for a particular patient. However, when this data is integrated with RNA-sequencing (RNA-seq) data from the same patient, it may be discovered that a variant in a non-coding region (an intron) is causing aberrant splicing, leading to the production of a non-functional protein. Studies have shown that this integrative approach can increase the diagnostic yield by 10-35% in cases that were not solved by WES alone [30]. This multi-omics approach allows researchers to trace the impact of a genetic mutation through multiple biological layers, from DNA to RNA to protein, and ultimately to its metabolic consequences.

B. Modeling Biological Networks and Their Dynamics

Systems biology allows for the development of computational models of biological networks, including protein-protein interaction networks (PPINs), to demonstrate how different biological constituents interact. From these interactions, it is possible to recognize key "hub" proteins that play important roles in ensuring that cellular networks are stable. Changes in these "hub" proteins tend to cause severe phenotypes of diseases [4]. Additionally, agent-based modeling can be employed to simulate how mitochondrias behave dynamically, giving insight into how mitochondrial dynamics, including transport, are affected in different diseases [31].

The integration of multi-omics approaches and network modeling has led to the development of various breakthroughs in the field of mitochondrial medicine. The application of systems biology approaches has helped in the identification of novel biomarkers for mitochondrial diseases. For example, the application of metabolomics approaches has helped in the identification of specific metabolic signatures associated with various mitochondrial defects that could be applied for diagnostic purposes. An example is the identification of increased circulating growth differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21), which are secreted from the muscle cells that are subjected to mitochondrial dysfunction. The two biomarkers are currently recognized for their application in the diagnosis of mitochondrial diseases, particularly those that are associated with myopathies [10]. The application of systems biology approaches has helped in the demonstration of the remodeling of metabolic pathways in mitochondrial diseases, thus opening the doors for novel therapeutic targets for the treatment of the diseases. An example is the demonstration that inhibition of the mammalian target of rapamycin (mTOR) signaling pathway, using rapamycin, a central regulator of growth and metabolic pathways, alleviates the severity of Leigh syndrome in mouse models and increases their lifespan [32]. The demonstration of the disruption of the one-carbon metabolic pathways has provided the basis for the application of therapeutic strategies that involve the folate metabolic pathways [10]. The application of the various approaches has provided the demonstration that, in the case of mitochondrial

diseases, not only is the nature of the disruption identified but also the manner in which the disruption occurs.

Case Studies: Applying Bioinformatics and Systems Biology to Specific Mitochondrial Diseases

To exemplify the potential of these new methodologies, the present study will analyze the paradigm shift in the understanding and diagnosis of a given mitochondrial disease through the application of bioinformatics and systems biology.

A. Leigh Syndrome

Leigh syndrome is a serious, progressive, and debilitating form of neurodegenerative disease, usually presenting in early childhood or infancy. It is a paradigm of the inherent difficulties in diagnosing mitochondrial diseases, given its notable genetic heterogeneity. Leigh syndrome is caused by mutations in over 75 different genes, located in both mitochondrial and nuclear DNA, resulting in a wide range of phenotypes. The role of bioinformatics in solving this conundrum has become pivotal. Whole-exome sequencing (WES) has become a first-line diagnostic option, as it can simultaneously screen all causative genes. Notably, a case study of a patient who was diagnosed with Leigh syndrome at three years of age, yet lacked a definitive genetic diagnosis for 15 years, was elucidated by investigators using WES. The study revealed that the cause of her illness was a compound mutation in the ECHS1 gene, consisting of a paternal missense mutation and a maternal deletion. The complex mutation mechanism was beyond the capabilities of traditional DNA sequencing. The use of bioinformatics was instrumental in terminating a long diagnostic odyssey for many patients [39]. Furthermore, by using a systems biology approach to understand the role of the ECHS1 protein in fatty acid metabolism, it is clear that it is not simply an energy deficit, but it opens up avenues for exploring treatment possibilities.

B. Leber's Hereditary Optic Neuropathy (LHON)

Leber's Hereditary Optic Neuropathy (LHON), unlike Leigh's Syndrome, is mainly associated with one of three most commonly occurring point mutations in the mitochondrial DNA (mtDNA). These mutations all affect the Complex I of the electron transport chain. On the one hand, the relative genetic homogeneity of the disease may be seen as a simplification of the pathogenesis of the disease. On the other hand, the exact mechanisms of the pathogenesis of the RGC death are not entirely understood despite the knowledge of the exact genetic mutation [35]. In this respect, the systems biology approach is particularly useful. Transcriptomics and metabolomics are used in cellular and animal models of the disease to understand the changes in the expression of the genes and the pathways in the RGCs that are dying in the disease. The aim is to identify the secondary mechanisms of pathogenesis of the disease and develop "mutation-independent" therapies that work by protecting the RGCs rather than correcting the mutation [36]. This approach has already led to the use of the antioxidant drug Idebenone and the development of the gene therapies that are in the pipeline for clinical trials [37].

C. Mitochondrial Cardiomyopathy

Cardiomyopathy is a phenotypic presentation of mitochondrial disease; however, many cases of cardiomyopathy, especially in the absence of associated systemic symptoms, are undiagnosed at the genetic level. Current genetic tests for cardiomyopathy do not include analysis of the mitochondrial genome. A recent publication has demonstrated the utility of using large-scale genomic datasets and specific bioinformatics pipelines. The authors have utilized whole-genome sequencing (WGS) from the 100,000 Genomes Project in the UK and a specific pipeline for the analysis of mtDNA, termed MitoHPC, for the analysis of mtDNA variants and have identified a pathogenic mtDNA variant in patients with hypertrophic cardiomyopathy (HCM) phenotypes that were not explainable at the genetic level. These variants would not have been identified without the specific pipeline for mtDNA analysis from the WGS results, which contain mtDNA variants in the background [37]. The importance of mtDNA analysis in all cases of cardiomyopathy is emphasized by the results of this publication and indicates the need for the expansion of first-line genetic tests for cardiomyopathy to include mtDNA analysis.

Challenges and Future Perspectives

Despite significant advances in mitochondrial medicine, as exemplified by advances in bioinformatics and systems biology, there are still challenges. The potential for future breakthroughs remains high.

A. Current Challenges

Even though the multi-omics approach promises a high analytical potential, the integration and interpretation of these complex data sets still represent a major challenge. It is a pressing issue to develop robust and standardized bioinformatics tools that can effectively integrate the heterogeneous data from various omics layers in a meaningful way [7]. It is also important to note that the identification of a genetic variant is only the first step in the process. The validation of the function to prove the pathogenicity of the variant is a time-consuming task. It is a labor-intensive task to perform high-throughput functional validation to match the rapid identification of variants. In conclusion, it is evident that the identification of effective therapy for patients with mitochondrial diseases is a major challenge. Even though the molecular basis of the diseases is expanding rapidly, the development of effective therapy is a major challenge. This is mainly due to the genetic and clinical heterogeneity observed in these diseases.

Furthermore, the rapid advancement of mitochondrial genetics brings forth significant ethical considerations. The use of preimplantation genetic diagnosis (PGD) and mitochondrial replacement therapy (MRT) to prevent the transmission of mtDNA diseases raises complex ethical, social, and legal questions. Issues such as the long-term safety of MRT, the creation of "three-parent babies," and the potential for germline modification necessitate ongoing ethical discourse and robust regulatory frameworks to ensure these technologies are used responsibly and equitably.

B. Future Directions

The future of mitochondrial medicine is expected to show a heightened use of artificial intelligence (AI) and machine learning. For instance, AI is currently being used to improve the accuracy of pathogenicity prediction tools, as seen in the use of APOGEE 2 [27]. The future of AI is expected to be used in developing predictive tools that will be able to estimate the probability of a patient having mitochondrial diseases based on their phenotypes, hence helping in decision-making in terms of genetic testing, consequently reducing its costs [38]. The other aim is to move beyond research studies into clinical applications by developing advanced multi-omics integrations. This will require developing strong, unifying algorithms that will be capable of integrating multi-omics data across different levels of omics to provide a comprehensive view of diseases in individual patients [39]. The newly emerging field of systems pharmacology aims at developing computational tools that integrate aspects of pharmacokinetics/pharmacodynamics with aspects of diseases. This could be used to simulate how future drugs could affect biological systems, hence accelerating drug discovery as well as helping in developing efficient drug trials.

C. The Dawn of Personalized Medicine

The final aim and objective of all this research is to better the life of patients with mitochondrial diseases. The knowledge obtained from this field of bioinformatics and systems biology is opening the door to a new horizon of personalized medicine, where the medicine and therapy are tailored according to the individual patient based on their unique genetic and molecular profile. The strategies that are emerging from this field are gene therapy, which corrects the genetic defect by introducing a normal gene or editing the gene itself. Another emerging field is mitochondrial replacement therapy, which replaces the patient's mitochondria with normal functioning mitochondria from another source. The third is drug repurposing, which uses drugs that have already been approved and have shown efficacy in the treatment and management of mitochondrial diseases. The profound knowledge obtained from the mechanisms and pathways at the individual level by employing these advanced methodologies is the key to the emerging field of personalized medicine. The "one-size-fits-all" approach is no longer sufficient; this is the time to hope and aim to provide better therapies and drugs to treat these debilitating and devastating diseases.

CONCLUSION

Fundamental Finding : The combination of bioinformatics and systems biology has led us to a major paradigm shift in the way we deal with mitochondrial diseases. We have progressed beyond the stage of simply identifying the various genetic mutations that lead to the diseases and have begun to understand the complex networks within cells and how they go wrong in the disease. We no longer think of the mitochondria simply as the energy producers of the cell but as part of a dynamic system that interacts in complex ways with other processes in the cell. **Implication :** Weaving together the various aspects of the data from the various "omics" sciences and computational models has not only

improved diagnosis but has led us towards precision and personalized medicine. Understanding the way in which the diseases develop at the molecular and system level is helping us move towards medicine that actually attacks the root of the disease and not simply the symptoms. **Limitation :** The future of patients suffering from mitochondrial diseases looks very promising, based on the close and collaborative work between clinicians, researchers, and data scientists as they unlock one of the most complex stories in the history of human genetics. **Future Research :** The future of patients suffering from mitochondrial diseases looks very promising, based on the close and collaborative work between clinicians, researchers, and data scientists as they unlock one of the most complex stories in the history of human genetics.

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