ejpmr, 2025, 12(3), 355-361

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

GENETIC ENIGMAS IN SOME RARE DISEASES

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Article Received on 19/01/2025 **Article Revised on 09/02/2025** **Article Accepted on 01/03/2025**

ABSTRACT

Rare diseases present unique challenges and opportunities for exploring genetic mechanisms and developing innovative therapies. This review examines the intricacies of genetic research in rare monogenic disorders With an emphasis on progress in conditions like Zellweger spectrum disorder (ZSD), cystic fibrosis (CF), and Huntington's disease (HD), each of these disorders highlights the complex relationship between genetic mutations and clinical symptoms, demonstrating how molecular discoveries can improve diagnostics and treatment strategies. Research on ZSD has revealed potential therapeutic options, including chaperone treatments designed to restore protein function. The treatment approach for CF has evolved from simply managing symptoms to adopting precision medicine, with CFTR modulators and emerging gene therapies offering transformative possibilities. For HD, advancements in RNA interference and antisense oligonucleotides present promising avenues for modifying disease progression. The review also addresses the ethical considerations surrounding genetics in rare diseases, such as informed consent, data privacy, equitable access, and the psychosocial impacts on patients and their families. These ethical concerns are vital as gene-editing technologies and personalized medicine continue to reshape the research landscape. In conclusion, this review underscores the importance of integrating genetic, molecular, and ethical viewpoints to enhance understanding, diagnostics, and treatments for rare diseases. Continued collaboration between researchers, clinicians, and policymakers will be essential in overcoming these challenges and turning discoveries into tangible benefits for patients.

KEYWORD: Genetic mechanisms, Monogenic disorders, Zellweger spectrum disorder (ZSD), Cystic fibrosis (CF), Huntington's disease (HD), Genetic mutations, Clinical outcomes, Molecular discoveries, Chaperone treatments, CFTR modulators, Gene therapies, CRISPR/Cas9, mRNA therapeutics.

1. INTRODUCTION

Genetic puzzles in rare diseases pose significant challenges for both researchers and clinicians. These conditions, often stemming from mutations in individual genes, offer important insights into the genetic causes of more prevalent complex disorders.[1] Investigating rare monogenic diseases has been crucial in uncovering the genetic foundations of various conditions, with genes like ABCC6 serving as examples that extend beyond their primary associated disorders.[1] The realm of psychiatric disorders, historically viewed as some of the most perplexing challenges in medicine, has experienced remarkable advancements in genetic research over the last five years. Investigations into conditions such as Zellweger spectrum disorder and Cystic fibrosis have generated new theories regarding their causes and provided insights into their genetic structures.[2,3] This progress underscores the potential of genetic research to illuminate the complexities of both rare and intricate disorders. Nonetheless, pinpointing the genetic factors of a disease can be quite complex. Take rheumatoid arthritis, for instance; reaching a consensus on its genetic contributions has been difficult, even with traditional methods like twin studies and family recurrence risk evaluations.[3] This challenge serves as a reminder that the journey to discovering genes linked to complex disorders is often filled with hurdles. A fascinating feature of many rare genetic disorders is their late onset, a trait also seen in several neurodegenerative diseases. Recent research using Alzheimer's mouse models has indicated that modifying the aging process through adjustments to the insulin/IGF signaling pathway can slow down disease progression and alleviate related impairments.[4] This discovery points to a possible therapeutic strategy for addressing late-onset neurodegeneration by focusing on the aging process itself.

2. Case Studies: Solving Genetic Mysteries

2.1 Zellweger Spectrum Disorder

Zellweger syndrome (ZS) is a rare genetic condition characterized by a severe decrease or complete absence of functional peroxisomes in cells, leading to significant biochemical and cellular disruptions. It belongs to the Zellweger spectrum disorders (ZSD), a group of autosomal recessive diseases linked to defects in

peroxisomal biogenesis, resulting from mutations in PEX genes. These disorders are classified as leukodystrophies, primarily affecting the brain's white matter and causing major neurological and systemic complications.[3] Zellweger syndrome (ZS) is named after Hans Zellweger (1909–1990), a Swiss-American pediatrician and geneticist from the University of Iowa, who made significant contributions to understanding the clinical and molecular aspects of this condition.[6] Molecular studies have revealed that mutations in PEX genes lead to peroxisomal dysfunction, interfering with metabolic processes like the degradation of very long-chain fatty acids (VLCFAs) and the synthesis of bile acids.[7] These metabolic disturbances lead to toxic metabolite accumulation, which underpins the disease's severe systemic manifestations. Clinically, ZS presents in the neonatal period with craniofacial dysmorphisms, profound hypotonia, seizures, liver dysfunction, and developmental delays. The prognosis is poor, with most patients succumbing within the first year of life.[5]

Zellweger spectrum disorders (ZSDs) comprise a diverse group of autosomal recessive conditions linked to peroxisomal biogenesis defects, caused by mutations in one of 13 PEX genes. These disorders impair peroxisome development, resulting in extensive metabolic dysfunction that affects both catabolic and anabolic processes. A key characteristic of ZSD patients is the accumulation of very long-chain fatty acids (VLCFAs), phytanic and pristanic acids, C27-bile acid intermediates, and pipecolic acid in the bloodstream, along with plasmalogen deficiency in red blood cells. Clinically, ZSDs present as a continuum of overlapping symptoms, with core manifestations including liver dysfunction, developmental delays, neurological impairments, adrenocortical abnormalities, and deficits in hearing and vision.[6] Zellweger spectrum disorders (ZSDs) were previously categorized into three separate conditions: Zellweger syndrome (ZS), Neonatal Adrenoleukodystrophy (NALD), and Infantile Refsum disease (IRD). These conditions are now understood to exist along a clinical spectrum, with ZS being the most severe form and IRD representing the mildest. More recently, Heimler syndrome, a milder peroxisomal biogenesis disorder, has been incorporated into this spectrum.[8]

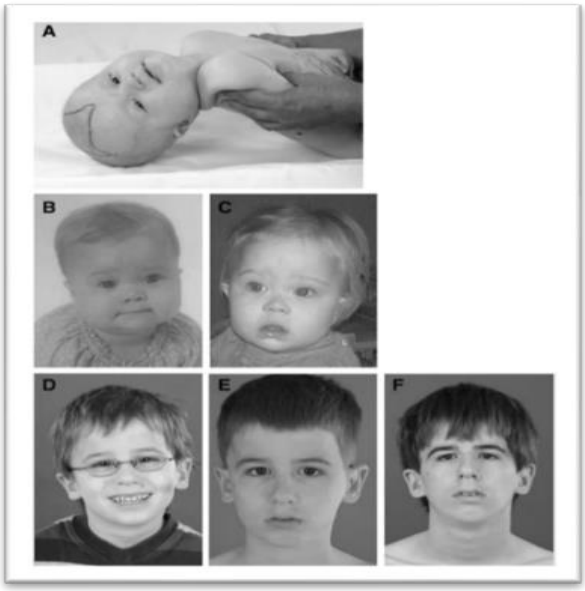

Fig.1: Progression of Craniofacial Features in Individuals with ZSD Over Time.

2.2 Cystic Fibrosis

Cystic fibrosis (CF) is an inherited disorder that leads to the production of thick, sticky mucus, primarily impacting the respiratory, digestive, and reproductive systems. It results from mutations in the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene. First identified in the 1930s by Dorothy Andersen, CF was originally called "cystic fibrosis of the pancreas" due to its impact on pancreatic function. The discovery of the CFTR gene in the late 1980s marked a major breakthrough in genetics, transforming both diagnosis and treatment approaches.[2]

Cystic fibrosis (CF) is the most common severe autosomal recessive genetic condition in Caucasians, affecting approximately 70,000 individuals worldwide.[10] First extensively documented in 1938 by D.H. Anderson, cystic fibrosis is characterized by impaired epithelial chloride transport and progressive lung disease.[11,12] The disorder is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes an epithelial anion channel.[13] Patients with CF experience excessive mucus buildup, which leads to serious clinical issues in the respiratory, gastrointestinal, and genitourinary systems.[12] The primary symptoms include disrupted airway surface hydration, persistent bacterial colonization, continuous inflammation, and gradual destruction of the airway wall structure.[14]

Moreover, individuals with CF have elevated electrolyte levels in their sweat, a feature that has become essential for diagnosis.[12] In summary, CF is a complex and life-limiting condition that necessitates a comprehensive management strategy. Although there has been considerable advancement in understanding and treating the disease since it was first identified, ongoing research is dedicated to developing targeted therapies, enhancing diagnostic methods, and addressing the psychological challenges faced by those with CF.[11,13,15]

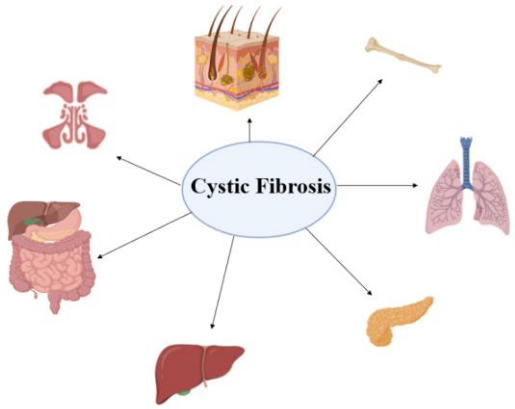

Fig.2: Multiple organ systems affected due to Cystic Fibrosis.

2.3 Huntington Disease

Huntington disease (HD) is a neurodegenerative disorder that progresses over time, inherited in an autosomal dominant pattern, and caused by a mutation that involves a CAG trinucleotide repeat expansion in the huntingtin (HTT) gene.[16,17] This genetic change causes an extended polyglutamine sequence in the huntingtin protein, leading to a range of motor, cognitive, and psychiatric symptoms that typically emerge in adulthood.[18,19] Interestingly, although HD is mainly recognized as an adult-onset condition, there exists a juvenile form that can affect children younger than 10 years, accounting for approximately 1-2% of all HD cases.[20] This early-onset variant is linked to larger CAG expansions and may exhibit distinct clinical characteristics, including rigidity, seizures, and learning disabilities.[20] In summary, HD is a key model for studying neurodegenerative disorders due to its singular genetic origin and the possibility of predicting its onset through genetic testing.[16] While no cure is available at this time, ongoing research aims to identify biomarkers for early detection and explore potential disease-modifying treatments.[16,21] The complex interactions between genetic, molecular, and environmental factors in the development of HD continue to be a central area of ongoing scientific investigation.[17,22]

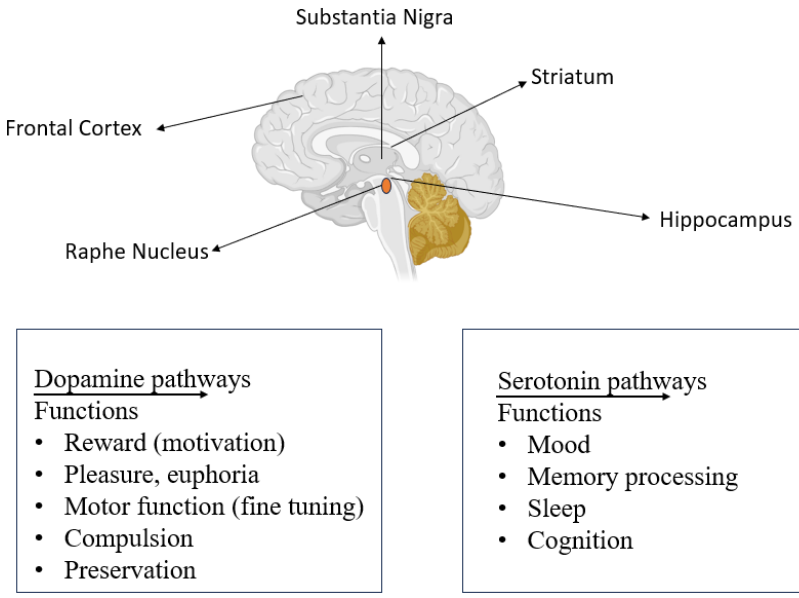

Fig. 3: Different Pathways of Brain.

3. Challenges in Research and Diagnosis

3.1 Zellweger Spectrum Disorder

Zellweger spectrum disorder (ZSD) is a multi-faceted condition which makes it difficult to conduct effective research as well as diagnosis. Diagnosis of patients can be extremely difficult due to the breadth and variety of their clinical manifestations including harsh neurological problems at birth stage or even degenerative diseases that span adulthood.[23] This makes genetic classification difficult as well, where the description of three phenotypes fails to explain the entire range of conditions present under this particular disorder.[24]

Another interesting point was Cohen's mention of the lack of literature on the developments surrounding new methods of screening newborns, this coupled with the hypothesis that genetic screening can help identify patients at an earlier stage.[23] The shortage of screening literature also points towards genetic deficiency being absent, with multiple PEX genes being responsible for the congenital

defect ZSD, finally adding a complication towards research(ZSD).[25] Likewise, while in one particular complementation group deficiency in PEX1 exon 13 is the most common defect, multiple other genetic disruptions in other genes this time around can cause ZSD.[25,26]

3.2 Cystic Fibrosis

In 2012, the U.S. Food and Drug Administration approved ivacaftor (Kalydeco) for individuals aged 6 and older with at least one G551D mutation. Today, it is authorized in the U.S. for treating cystic fibrosis (CF) patients aged 2 and older who have one of 38 CFTR gene mutations known to respond to ivacaftor. This medication is designed to target a non-functional but correctly localized CFTR protein, helping to open the chloride channel in CF cells. Clinical trials showed no safety concerns, and the treatment groups achieved the primary goal of improved lung function, along with secondary goals of fewer pulmonary exacerbations, weight gain, and enhanced quality of life. In 2015, The combination of ivacaftor and lumacaftor (Orkambi) was initially approved for individuals aged 12 and older who are homozygous for the F508del mutation. In 2016, the approved age limit was reduced to 6 years. Lumacaftor works by helping to transport defective CFTR protein to the correct location in the airway cell membrane, thereby improving its function as a chloride channel. In 2020A new combination therapy consisting of ivacaftor, tezacaftor, and elexacaftor (Trikafta) received approval for individuals aged 12 and older with at least one copy of the F508del mutation. In 2021, its approval was extended further, this approval was extended to children aged 6 and up. Both tezacaftor and elexacaftor are designed to correct the folding of the CFTR protein. Nearly 90% of CF patients qualify for either Kalydeco, Orkambi, or Trikafta based on their CF mutations. However, there remains an unmet medical need for the remaining 10% of the global CF population, which is approximately 105,000 individuals. Companies are actively working on developing new combination therapies to meet the needs of about 10% of CF patients who do not have at least one F508del mutation, the most common CF-causing variant worldwide, as well as exploring gene therapies that could potentially address all mutations.[27]

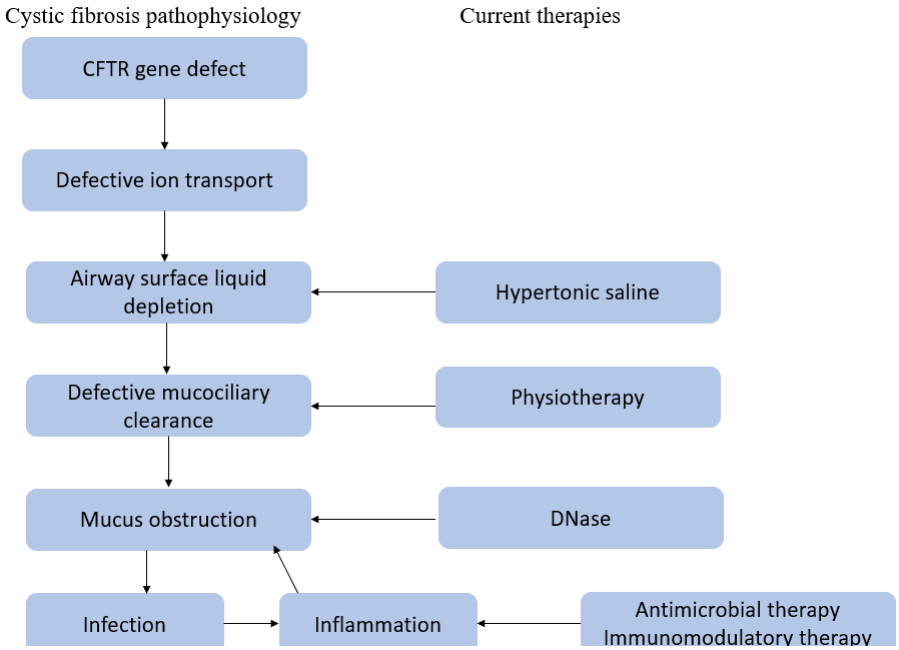

Fig.4: Pathophysiology and Current Therapies for Cystic Fibrosis.

3.3 Huntington Disease

Research and diagnosis of Huntington disease (HD) encounter numerous challenges, mainly due to the disease's complex nature and its late-onset characteristics. The genetic basis of HD involves an expansion of CAG repeats in the huntingtin gene, offers both opportunities and hurdles in creating effective diagnostic and treatment strategies.[28] A significant challenge in HD research is the quest for effective therapies that can alter disease progression instead of merely managing symptoms. Current treatments for neurodegenerative disorders, including HD, primarily focus on symptom management, with limited success in changing the disease's trajectory.[29] The rise of bioactive peptides as potential therapeutic agents is promising, yet there are considerable obstacles in their development and delivery to the brain.[29] Interestingly, although genetic testing for HD is accessible, awareness about predictive testing among at-risk individuals is surprisingly low. A study found that many individuals with limited knowledge about predictive testing still planned to undergo it, highlighting the importance of improved genetic counseling and education.[30] Furthermore, the emotional and psychological effects of genetic testing on young adults present unique challenges, necessitating flexible and personalized genetic counseling approaches.[31] In summary, the challenges in HD research and diagnosis range from developing therapies that modify the disease to

addressing the psychological effects of genetic testing. The complexity of the disease requires a comprehensive approach, including better genetic counseling, the development of innovative therapeutic strategies like RNA interference and bioactive peptides, and the identification of reliable biomarkers for early diagnosis and treatment monitoring.[28] Future research should aim to tackle these challenges to enhance the quality of life for those affected.

4. Therapeutic Approaches and Future Direction

As reported by Klouwer et al.[24], At present, no cure exists for Zellweger spectrum disorders (ZSDs), and the primary approach to treatment is supportive care. However, recent research advancements have opened up new possibilities for future therapeutic interventions. One promising strategy is the development of chaperone treatments. In cells carrying the common PEX1-p.Gly843Asp mutation, a high-content screening approach experiment identified drugs that may help partially restore matrix protein import, suggesting that chaperone therapy could be a viable option for this misfolded protein.[32] This finding presents a potential pathway for creating personalized treatments for ZSD patients with specific mutations. Some biochemical abnormalities in patients with ZSD may improve as they age. A study found that peroxisomal biomarkers that were abnormal in childhood can sometimes return to normal in adulthood, suggesting that the disease does not progress in a straight line.[33] Although treatment is still primarily supportive, ongoing research provides hope for targeted therapies, including compounds aimed at restoring peroxisome function.

Since the CFTR gene was identified in 1989, treatments for cystic fibrosis have evolved significantly. Initially focused on managing symptoms like bacterial infections and mucus buildup[34], the approach has shifted towards correcting the underlying ion transport defect to restore CFTR function, stimulate alternative chloride channels, and rehydrate the airways.[34,35] CFTR modulators, such as ivacaftor for the G551D mutation, are designed to correct defective CFTR proteins, marking a significant step in precision medicine.[36,37] Additionally, innovative strategies like gene therapies (CRISPR/Cas9, mRNA therapeutics) show great promise. Continued collaboration will be essential for further advancements.

Huntington's disease (HD) is a neurodegenerative condition inherited in an autosomal dominant manner, resulting from an expansion of CAG repeats in the HTT gene.[38,39] While current treatments primarily aim at managing symptoms, there is significant progress in developing therapies that could modify the disease. These include strategies for lowering huntingtin levels, modulating neuroinflammation, and improving synaptic transmission (Caron et al., 2018). Innovations in RNA interference and antisense oligonucleotides present new ways to decrease the levels of the mutant protein.[38] Research is actively exploring gene and cell therapies, methods to lower huntingtin, and enhanced protein clearance techniques, with several clinical trials currently underway. These initiatives hold the potential to transform the treatment landscape for HD and may also have implications for other neurodegenerative diseases.[39, 40]

5. Ethical Consideration in Rare Disease Genetics

Rare disease genetics poses distinct ethical challenges due to the limited number of patients, intricate diagnostic processes, and the consequences for individuals and their families. Important considerations include:

5.1 Informed Consent and Genetic Testing

Obtaining informed consent for genetic testing is essential, especially for predictive testing and whole-genome sequencing, as these tests may uncover incidental findings or future health risks.[41] Patients need to fully grasp the implications of the results for themselves and their relatives.

5.2 Privacy and Data Sharing

While sharing genetic data is crucial for advancing research, it also raises significant privacy concerns. Striking a balance between maintaining patient confidentiality and fostering collaborative research is a major ethical challenge.[42]

5.3 Equitable Access: Diagnostics and treatments for rare diseases are frequently costly and not readily available to underserved communities. Ethical frameworks should address the disparities in access to genetic services and new therapies.[43]

5.4 Psychosocial Impact: A genetic diagnosis can have significant emotional, social, and financial impacts on patients and their families, emphasizing the importance of adequate genetic counseling and support.[44]

5.5 Research and Therapeutic Development: Ethical issues in rare disease research encompass fair recruitment of participants, ensuring benefit-sharing, and managing conflicts of interest, particularly with the emergence of gene-editing technologies.[45]

5.6 Reproductive Decision-Making: Genetic information can affect reproductive decisions, raising ethical dilemmas regarding prenatal testing, selective termination, and the risk of stigmatization or discrimination.[46]

CONCLUSION

Although rare diseases are uncommon, they offer crucial insights into genetics and disease mechanisms, contributing to the advancement of innovative treatments.This review examines Zellweger spectrum disorder (ZSD), cystic fibrosis (CF), and Huntington's disease (HD), emphasizing how genetic mutations influence clinical outcomes and treatment approaches. Recent advancements such as chaperone therapies for ZSD, CFTR modulators for CF, and RNA interference for HD showcase the progress being made in precision medicine and gene therapies. However, challenges remain, including the complexity of phenotypes, genetic diversity,

and ethical issues like informed consent, privacy, and fair access to treatments. Tackling these challenges necessitates a comprehensive approach that combines genetic, molecular, and ethical considerations, along with collaboration among all stakeholders. As precision medicine continues to advance, the future of rare disease research is filled with potential, offering hope for groundbreaking diagnostics and therapies that can enhance patient outcomes and meet previously unmet medical needs.

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