AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 3, Issue 12, 2025 ISSN (E): 2993-2149

The Role of Protein Synthesis Disorders in Hereditary Diseases (Literature Review)

Jasmina G. Obidovna, Farizakhon I. Ozodkhonovna
Student of Tashkent State Medical University, Tashkent, Uzbekistan

Nurkhan Kh. Mukhamedova
Department of Medical and Biological Chemistry Professor of Tashkent State, Medical University, Tashkent, Uzbekistan

Abstract: This article analyzes the causes, molecular mechanisms, and clinical manifestations of hereditary diseases resulting from protein synthesis disorders. Genetic mutations disrupt various stages of protein synthesis—transcription, translation, and posttranslational modifications—as a result of which vital proteins are not produced in sufficient quantities or in the correct structure in the body. The article highlights the pathological consequences of these processes using the examples of diseases such as phenylketonuria, cirrhosis, cystic fibrosis, and Hemophilia. The study reveals the role of protein synthesis disorders in the pathogenesis of hereditary diseases and the possibilities of early diagnosis and gene therapy in medicine.

Keywords: protein synthesis, gene mutation, genetic disease, translation, phenylketonuria, gene therapy.

Introduction

Proteins are essential macromolecules responsible for almost every vital function in the human body, including enzymatic reactions, hormonal regulation, immune defense, and maintenance of cellular structure. Their biosynthesis consists of precisely regulated stages — DNA transcription, mRNA processing, translation on ribosomes, and post-translational modifications. A mutation or structural defect at any of these levels disrupts the formation of normal protein molecules and becomes a direct cause of hereditary diseases [1,2].

Genetic mutations may alter the coding sequence of a gene, impair mRNA splicing, change ribosomal activity, or lead to misfolding and degradation of newly synthesized polypeptides. As a result, cells lose metabolic stability, accumulate toxic intermediates, and develop oxidative stress. Well-known hereditary diseases—including phenylketonuria, cystic fibrosis, β-thalassemia, hemophilia, and Duchenne muscular dystrophy—are all directly linked to abnormalities in protein biosynthesis [3]. Experimental studies show that protein synthesis disorders do not always originate from nuclear DNA alone. Mutations in mitochondrial DNA impair synthesis of mitochondrial enzymes and lead to cardiomyopathy, optic atrophy, and neuromuscular degeneration [4,5].

In addition, failure of the ubiquitin-proteasome system or chaperone proteins results in intracellular accumulation of misfolded proteins, which has been observed in metabolic and neurodegenerative conditions [6]. The term “ribosomopathies” has recently entered medical genetics, describing diseases caused by defects in ribosomal proteins or rRNA processing, such

as Diamond-Blackfan anemia and Shwachman-Diamond syndrome [7]. These discoveries confirm that almost every stage of protein synthesis can be a potential source of hereditary pathology.

Early diagnosis plays a decisive role in preventing irreversible complications, especially in newborns. Modern approaches include enzymatic assays, tandem mass spectrometry for newborn screening, whole-exome sequencing, and targeted gene panels that identify the exact mutation responsible for protein synthesis failure [8,9]. In recent years, gene-editing technologies such as CRISPR-Cas9, mRNA-based therapy, and recombinant enzyme replacement have opened promising therapeutic perspectives, proving that correction of defective protein synthesis is becoming clinically achievable. Therefore, studying protein synthesis disorders has major scientific and clinical significance. Understanding how mutations affect transcription, translation, and post-translational modification allows clinicians and researchers to develop early diagnostic programs, design targeted therapies, and prevent severe hereditary diseases[10,11].

Disorders at the Translation Stage Translation is the second essential stage of protein synthesis, during which the nucleotide sequence of mRNA is converted into a polypeptide chain with the participation of ribosomes, tRNA, aminoacyl-tRNA synthetases, and translation factors. This stage requires strict accuracy: even a single amino acid substitution may alter protein structure, stability, or enzymatic activity. Mutations affecting the translation process lead to reduced protein production, synthesis of truncated polypeptides, or formation of misfolded and toxic proteins [1,2]. Translation defects develop due to mutations in ribosomal protein genes, deficiency of tRNA or aminoacyl-tRNA synthetases, errors in codon recognition, abnormal activation of initiation or elongation factors, and premature stop-codons that lead to instability of mRNA [3,7]. A well-known example of translation defects is cystic fibrosis. The CFTR gene mutation ΔF508 causes incorrect folding of the protein during translation. As a result, chloride channels do not reach the cell membrane, which leads to thick mucus, chronic lung infections, pancreatic insufficiency, and male infertility. More than 2,000 CFTR mutations have been described, and a large part of them are associated with disturbances in translation efficiency [4,5,6].

Another example is phenylketonuria. Although the primary mutation lies in the PAH gene, the main pathogenic mechanism is incorrect folding of the enzyme during translation. Misfolded PAH is rapidly degraded, which leads to accumulation of toxic phenylalanine metabolites and severe neurological damage. The development of chaperone therapy has significantly improved clinical outcomes in phenylketonuria [8]. A separate group of hereditary diseases caused by translation defects are ribosomopathies, which develop due to impaired ribosome biogenesis. Diamond–Blackfan anemia, Shwachman–Diamond syndrome, and Treacher Collins syndrome are typical examples. These disorders affect not only protein synthesis, but also cell growth, immunity, and skeletal development [12].

Mitochondrial translation disorders form another important class of pathology. Since mitochondria have their own mRNA and ribosomes, mutations in mitochondrial rRNA or tRNA genes impair synthesis of respiratory chain enzymes. This leads to cardiomyopathy, optic neuropathy, lactic acidosis, and progressive neuromuscular degeneration The clinical consequences of translation defects include reduced enzyme activity, energy deficiency, toxic protein aggregation, metabolic failure, and neurodegeneration. For instance, in spinal muscular atrophy reduced production of SMN protein leads to motor neuron death and progressive muscle wasting. Modern mRNA-based therapy increases SMN protein levels and improves survival. Diagnostic methods include whole-exome sequencing, which identifies mutations of tRNA-synthetases and ribosomal protein genes; proteomic analysis to determine absence of specific proteins; western blotting and mass spectrometry to detect misfolded protein accumulation; and targeted newborn screening for diseases such as cystic fibrosis, spinal muscular atrophy, and

phenylketonuria. Early detection allows clinicians to start treatment before irreversible organ damage develops. [13,14].

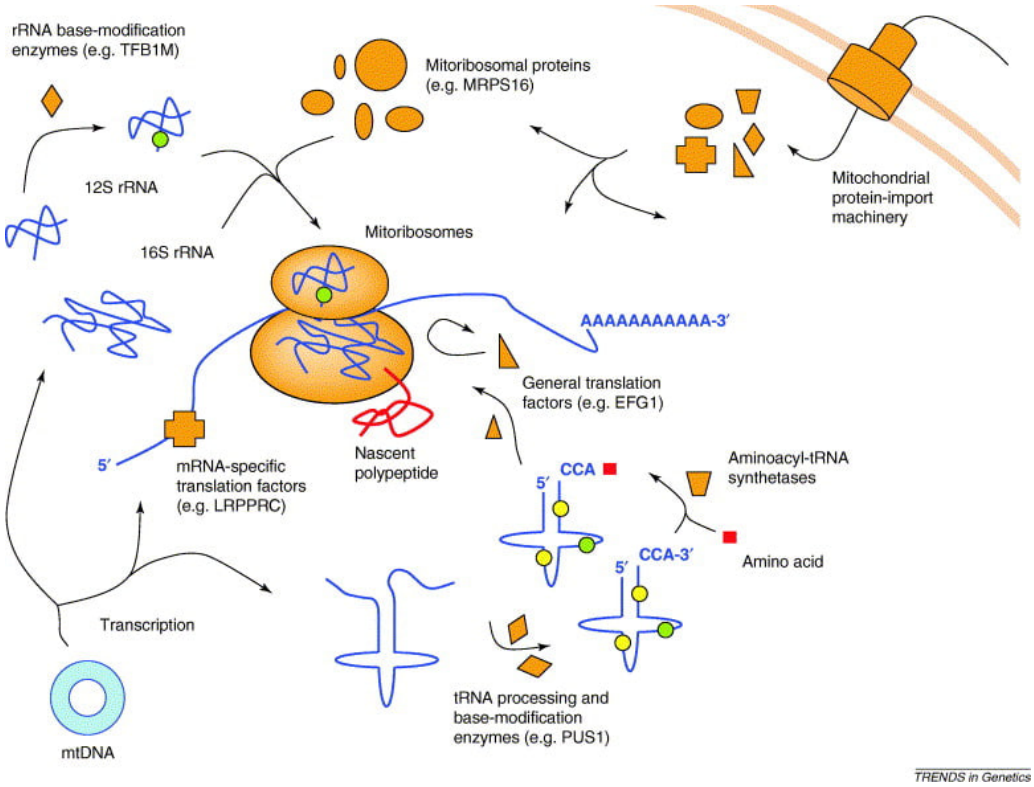

Figure 1. Nuclear genes and mitochondrial translation: a new class of genetic disease: Trends in Genetics.

Translation disorders therefore represent an important class of hereditary diseases that affect metabolism, development, and organ function. Advances in molecular diagnostics and therapy provide new possibilities to restore protein synthesis and improve the prognosis for affected patients. Disorders at the Post-Translational Modification Stage Post-translational modification is the final stage of protein synthesis during which newly formed polypeptides acquire correct three-dimensional structure, stability, biological activity, and intracellular localization. This process includes protein folding, glycosylation, phosphorylation, acetylation, and disulfide bond formation. Disturbances in these mechanisms lead to formation of unstable, inactive, or toxic proteins. A characteristic feature of post-translational defects is the accumulation of misfolded proteins inside the cell. Normally, chaperone proteins ensure proper folding, while the ubiquitin-proteasome system removes defective proteins. When these systems fail, protein aggregates accumulate and damage cells. Phenylketonuria is a classic example. Mutations in the PAH gene lead to synthesis of a structurally unstable enzyme that is rapidly degraded. As a result, phenylalanine and its toxic metabolites accumulate, causing neurological damage.

Chaperone therapy and tetrahydrobiopterin help stabilize the PAH protein and improve metabolic control. Cystic fibrosis is also associated with post-translational defects. In many patients, CFTR protein is synthesized but does not pass quality control in the endoplasmic reticulum and undergoes degradation.

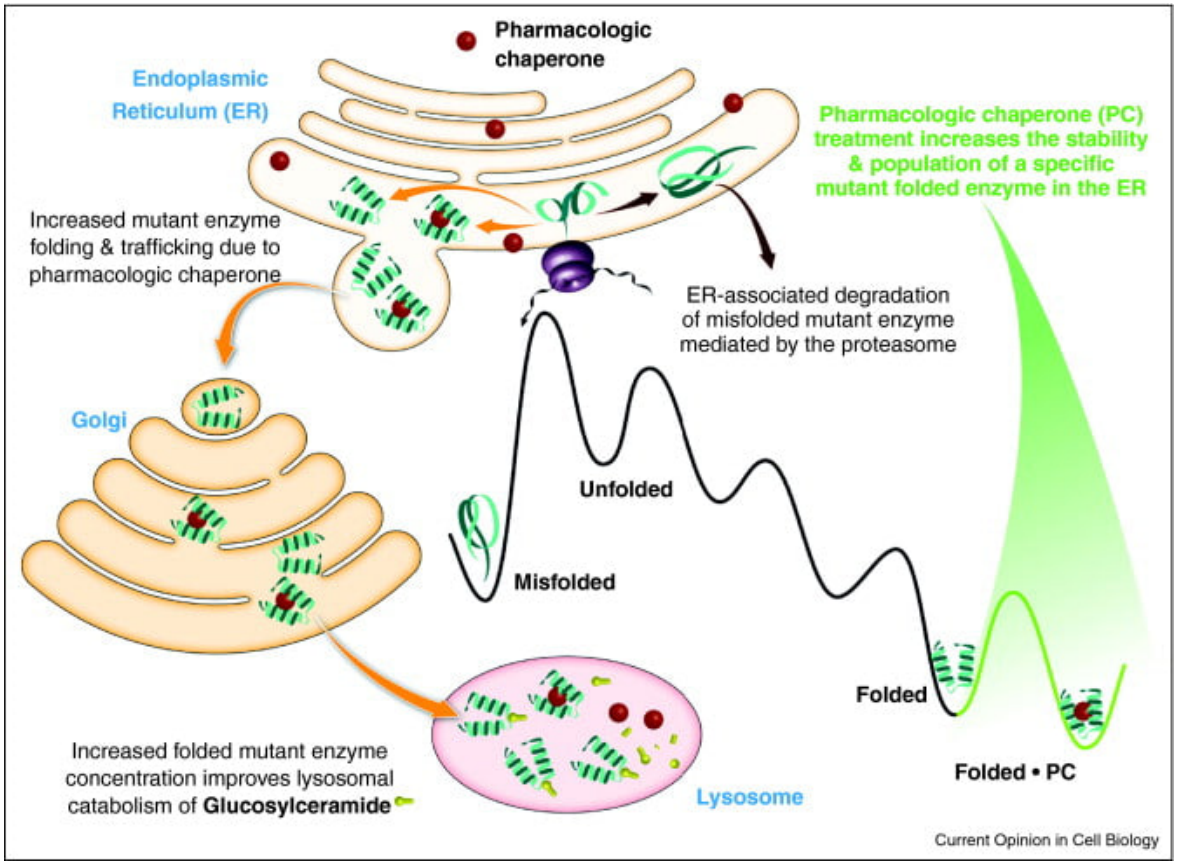

Figure. Pharmacological Chaperone - an overview

As a consequence, chloride channels do not reach the cell membrane, which leads to impaired ion transport and systemic clinical symptoms. Another group of disorders includes congenital defects of glycosylation. Mutations in glycosyltransferase enzymes disrupt normal protein glycosylation. These diseases cause growth retardation, immune deficiency, liver dysfunction, and neurological disorders. More than 130 genetic forms of glycosylation disorders have been described [6,7,8].

Post-translational modification is also essential for blood-clotting proteins. In hemophilia A and B, factor VIII or IX becomes unstable after synthesis, resulting in reduced clotting activity and spontaneous bleeding. Recombinant clotting factors are used to restore protein function and prevent hemorrhagic complications. Diagnosis of post-translational defects includes enzyme activity tests, mass spectrometry, western blotting, and glycosylation analysis. Treatment methods include enzyme replacement therapy, chaperone therapy, and gene-based approaches aimed at restoring production of correctly folded proteins. Thus, even if transcription and translation remain intact, failure of post-translational modification leads to severe metabolic, hematological, and neurological disorders [9,15].

Clinical Consequences of Protein Synthesis Disorders

Disorders of protein synthesis cause a wide spectrum of clinical manifestations, because almost every biochemical pathway in the human body depends on the function of structural and enzymatic proteins. When protein quantity or quality is reduced, metabolic control is disrupted, cellular homeostasis is lost, and organ structure becomes damaged. Clinical symptoms vary depending on which stage of protein synthesis is affected and which organs rely on the defective protein. A common consequence of enzyme deficiency is accumulation of toxic metabolites. In phenylketonuria, lack of functional PAH enzyme leads to high levels of phenylalanine, which causes severe intellectual disability, seizures, and developmental delay if untreated. Early screening and dietary therapy prevent irreversible brain damage structural protein defects lead to tissue instability and progressive damage.

In Duchenne muscular dystrophy, absence of dystrophin disrupts muscle fiber membranes and causes chronic inflammation, muscle degeneration, cardiomyopathy, and respiratory failure. Similar structural defects are seen in connective tissue disorders affecting fibrillin or collagen synthesis .In cystic fibrosis, defective CFTR protein causes impaired chloride transport and thick secretion in the lungs and gastrointestinal tract. This results in chronic lung infections, pancreatic insufficiency, malabsorption, and infertility. Long-term complications include bronchiectasis, pulmonary hypertension, and liver disease.

Hematological complications are also common. In β-thalassemia, decreased synthesis of hemoglobin causes chronic anemia, bone deformities, heart failure, and splenomegaly. In hemophilia, instability of clotting proteins leads to spontaneous bleeding, joint damage, and severe hemorrhage after minor injuries. Neuromuscular manifestations occur when protein synthesis defects affect nervous tissue. In spinal muscular atrophy, reduced SMN protein leads to progressive motor neuron loss, muscle weakness, and respiratory insufficiency. In mitochondrial translation disorders, deficiency of respiratory chain enzymes causes lactic acidosis, neuropathy, vision loss, and multi-organ failure. Protein misfolding and aggregation may also trigger chronic inflammation and oxidative stress, leading to cell death and organ dysfunction. In severe cases, this mechanism causes neurodegeneration, cardiomyopathy, immune deficiency, liver failure, or endocrine disorders. The severity of clinical outcomes depends on mutation type, residual protein activity, age of onset, and effectiveness of treatment. Early diagnosis and molecular therapy significantly improve prognosis and help prevent irreversible complications. Diagnostics and Modern Treatment Approaches Early diagnosis of protein synthesis disorders is critical, because many of these diseases lead to irreversible organ damage if treatment is delayed. Modern laboratory and genetic technologies make it possible to detect mutations, identify defective proteins, and monitor disease progression before clinical symptoms become severe.

Diagnostic approaches depend on the molecular mechanism of the disorder. Polymerase chain reaction and sequencing methods are used to identify mutations in promoter regions, coding sequences, and splicing sites. Whole-exome and whole-genome sequencing allow simultaneous analysis of thousands of genes, which is especially important for newborns with severe metabolic or neuromuscular symptoms. Rapid genomic testing is increasingly used in neonatal intensive care units to identify treatable genetic conditions .

Biochemical tests are used to measure enzyme activity and detect toxic metabolites. For example, elevated phenylalanine confirms phenylketonuria, reduced CFTR function confirms cystic fibrosis, and abnormal hemoglobin chains indicate β-thalassemia. Mass spectrometry and proteomic analysis help detect misfolded proteins, absence of specific protein isoforms, or abnormal glycosylation patterns [5,7]. Newborn screening programs play a major role in early detection. Many countries include cystic fibrosis, phenylketonuria, spinal muscular atrophy, and congenital glycosylation disorders in national screening systems. Early identification allows treatment to begin before organ damage develops.

Therapeutic strategies depend on the type of protein defect. In metabolic diseases, dietary therapy or enzyme replacement reduces toxic metabolite accumulation. In phenylketonuria, strict dietary control and tetrahydrobiopterin improve metabolic balance. In cystic fibrosis, CFTR modulators increase the stability or activity of misfolded proteins and improve lung function. In hemophilia, recombinant clotting factors prevent hemorrhage and joint damage .Gene therapy is one of the most promising directions in modern medicine. CRISPR-based genome editing, viral vector delivery, and mRNA replacement therapy allow cells to produce functional proteins instead of defective ones. Successful clinical trials have been conducted for spinal muscular atrophy, β-thalassemia, and hemophilia. In some patients, gene therapy reduces the need for lifelong medication and significantly improves quality of life [15].

Chaperone therapy and proteasome regulators are used to improve folding and increase the stability of partially functional proteins. Stem-cell transplantation and organ replacement are considered in severe cases where irreversible tissue damage has occurred. Modern diagnostics

and treatment approaches increase survival, improve metabolic control, and reduce complications. Early identification and targeted therapy offer new opportunities for managing hereditary disorders of protein synthesis and preventing long-term disability.

Conclusions

Disorders of protein synthesis represent one of the major causes of hereditary diseases and metabolic abnormalities. These defects may occur at different molecular stages, including transcription, translation, and post-translational modification. Regardless of the mechanism, the result is insufficient production of functional proteins, accumulation of toxic metabolites, cellular damage, and progressive organ dysfunction. Clinical manifestations range from metabolic disorders and anemia to neuromuscular degeneration and multi-organ failure. Early recognition of these disorders is essential, because timely treatment prevents irreversible complications. Modern diagnostic methods, such as DNA sequencing, newborn screening, enzyme activity tests, proteomic analysis, and mass spectrometry, allow detection of pathological changes before symptoms become severe.

Therapeutic strategies continue to advance. Dietary interventions, enzyme replacement therapy, proteasome regulation, chaperone treatment, and recombinant protein therapy improve metabolic stability and reduce morbidity. Gene therapy, including viral vector delivery, mRNA replacement, and CRISPR-based genome editing, offers a fundamental approach for correcting defective genes and restoring protein synthesis. Thus, a better understanding of the molecular mechanisms of protein synthesis disorders helps improve diagnostic accuracy, optimize treatment, and develop effective strategies for prevention. Continued progress in molecular genetics and biotechnology provides hope that many hereditary diseases will eventually become curable.

References:

1. Berg J.M., Tymoczko J.L., Gatto G.J., Stryer L. Biochemistry. – New York: W.H. Freeman, 2019. – 1050 p.
2. Bird A. DNA methylation patterns and epigenetic memory // Genes & Development. – 2002. – Vol. 16, №1. – P. 6–21.
3. Blau N., Van Spronsen F.J., Levy H.L. Phenylketonuria // Lancet. – 2010. – Vol. 376. – P. 1417–1427.
4. Chakraborty P., Anderson J.S., Naylor S.L. Ribosome biogenesis disorders // Human Molecular Genetics. – 2021. – Vol. 30, №5. – P. 108–119.
5. Cutting G.R. Cystic fibrosis genetics: from molecular understanding to clinical application // Nature Reviews Genetics. – 2015. – Vol. 16. – P. 45–56.
6. Emery A.E.H. The muscular dystrophies // The Lancet. – 2002. – Vol. 359, №9307. – P. 687–695.
7. Galanello R., Origa R. Beta-thalassemia // Orphanet Journal of Rare Diseases. – 2010. – Vol. 5, №11. – P. 1–15.
8. Gorman G.S., Schaefer A.M., McFarland R. Mitochondrial diseases // The Lancet. – 2016. – Vol. 3, №388. – P. 309–321.
9. Keown K., Brownlee K., Lau S. CFTR mutations: classification and clinical impact // Frontiers in Pediatrics. – 2020. – Vol. 8. – P. 1–12.
10. Kingsmore S.F. Rapid genome sequencing in newborns // JAMA. – 2020. – Vol. 324, №12. – P. 1202–1211.
11. Mendell J.R., et al. Gene therapy for spinal muscular atrophy // New England Journal of Medicine. – 2017. – Vol. 377. – P. 1713–1722.

12. Mills E.W., Green R. Ribosome biogenesis and disease // Nature Reviews Molecular Cell Biology. – 2017. – Vol. 18. – P. 341–355.
13. Narla A., Ebert B.L. Ribosomopathies: human disorders of ribosome dysfunction // Blood. – 2010. – Vol. 115, №16. – P. 3196–3205.
14. Nelson D.L., Cox M.M. Lehninger Principles of Biochemistry. – New York: W.H. Freeman, 2017. – 1200 p.
15. Taylor R.W., Turnbull D.M. Mitochondrial DNA mutations in human disease // Nature Reviews Genetics. – 2015. – Vol. 6, №5. – P. 389–402.