Balkan Med J 2025;42:92-3

The Importance of Genetic Diagnosis in Rare Diseases

Hakan Gürkan[1], Nihan Bilge Satkın[1,2]

[1]Department of Medical Genetics, Trakya University Faculty of Medicine, Edirne, Türkiye
[2]Department of Genetics and Bioengineering, Trakya University Faculty of Engineering, Edirne, Türkiye

Although rare diseases impact a small number of individuals, they lack a universally accepted definition. In the European Union (EU), a disease is classified as rare if it affects no more than 5 in 10,000 people. To date, more that 7,000 rare diseases have been identified, highlighting their significant global impact. Approximately 30 million people in the United States, 29 million in the EU (2008), and an estimated 400 million individuals worldwide are affected by various rare diseases.[1-5]

Approximately 80% of rare diseases are genetic in origin.[6,7] Of these, approximately 70% manifest during childhood, with approximately 3% manifesting in the neonatal period. Approximately 95% of rare diseases lack an approved treatment protocol. Thus, these patients are administered only symptomatic care.[2] Accurately diagnosing a rare disease can significantly improve disease management, help identify potential treatments, and prevent unnecessary interventions that may cause serious side effects. The time taken for diagnosing rare diseases varies widely, ranging from months to decades, and it depends on the patient's phenotype, patient's age, and available resources. The average time taken to reach a correct diagnosis is reportedly approximately 4-8 years. Approximately 30% of children with rare diseases die before reaching the age of 5.[8-12] The diagnostic process often involves various challenges, placing significant pressure and psychological stress on the patients and their families. Among these challenges are unequal access to essential healthcare services, the high costs of medical care, and the lack of coverage for these expenses by social security institutions.[1]

In inherited rare diseases, determining the genetic anomaly responsible for the condition and its mode of inheritance provides valuable insight into both the treatment options as well as the risk of passing on the disease to future generations.[13] However, some rare diseases may also arise from de novo mutations that affect only the individual.[5]

Early diagnosis of a rare disease can minimize the need for additional invasive and expensive tests, as well as alleviate the psychological burden on the patients and their families that is caused by living with an undiagnosed condition.[14] Furthermore, identifying the underlying genetic issue may serve as a valuable screening tool, which may enable the detection of symptomatic individuals, carriers, and asymptomatic individuals. This plays a crucial role in the secondary prevention of both benign and malignant diseases.[1] Until the early 2000s, genetic testing was expensive, difficult to access, and typically limited to the analysis of only a few genes at a time. Over the past two decades, advancements in genetic testing, particularly the development and adoption of next-generation sequencing (NGS) technologies, have significantly improved the affordability, reliability, and efficiency of genetic testing. The widespread use of NGS has enabled the identification of numerous previously undiagnosed diseases via whole exome sequencing (WES), which focuses on the protein-coding regions that make up 1.2% of the genome.[14] Trio WES (exome sequencing of parent-child trios), instead of singleton WES in a cohort of children with unaffected parents, reportedly reduces candidate variants for disease diagnosis by tenfold. A meta-analysis of five studies compared the diagnostic efficiency of whole genome sequencing (WGS) and WES in individual probands and cohorts with that of trio WGS and WES. The results indicated that the diagnostic probability of the trio approach was twice as high as that of single tests. For rare diseases that cannot be diagnosed via WES or WGS, diagnosis should be determined using complementary technologies such as transcriptome sequencing. Furthermore, based on the patient's phenotype, additional profiling methods such as metabolomic, proteomic, or epigenetic (e.g., methylation or histone acetylation) analyses should be considered. For patients who remain undiagnosed despite these efforts, periodic reanalysis of genomic data, particularly for variants of unknown clinical significance, is of critical importance. Furthermore, functional studies using in vitro and in vivo models should be undertaken to establish causality and elucidate the molecular mechanisms underlying novel variants, de novo variants, or variants of unknown clinical significance.[2,6-8]

Due to the lower economic appeal of developing drugs for rare diseases than drugs for common diseases, policies and legislation have been established to encourage the development of treatments for rare

Corresponding author: Hakan Gürkan, Department of Medical Genetics, Trakya University Faculty of Medicine, Edirne, Türkiye
e-mail: hakangurkan@trakya.edu.tr

Available Online Date: March 03, 2025 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-270125
Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: H.G. 0000-0002-8967-6124; N.B.S. 0000-0003-2257-4294.

Cite this article as: Gürkan H, Satkın NB. The Importance of Genetic Diagnosis in Rare Diseases. Balkan Med J.; 2025; 42(2):92-3.

diseases, which are known as orphan drugs. The Orphan Drugs Act of 1983 in the United States introduced various incentives, resulting in the approval of hundreds of orphan drugs. This legislation also inspired the adoption of similar laws in several European countries. Additionally, promising new treatment strategies, such as gene therapy, have brought hope to patients with genetically inherited rare diseases and their families.[14,15]

Authorship Contributions: Concept- H.G., N.B.S.; Design- H.G., N.B.S.; Data Collection or Processing- H.G., N.B.S.; Analysis or Interpretation- H.G., N.B.S.; Literature Search- H.G., N.B.S.; Writing- H.G., N.B.S.

Conflict of Interest: No conflict of interest was declared by the authors.

REFERENCES

1. Kruse J, Mueller R, Aghdassi AA, Lerch MM, Salloch S. Genetic testing for rare diseases: a systematic review of ethical aspects. *Front Genet.* 2022;12:701988. [CrossRef]
2. The Lancet Global Health. The landscape for rare diseases in 2024. *Lancet Glob Health.* 2024;12:e341. [CrossRef]
3. Global Genes (2020). *Rare Facts.* (Accessed June 1, 2020). [CrossRef]
4. European Union. "European Commission," in Communication from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's Challenges (Brussels: COM); 2008;679. [CrossRef]
5. Eurordis. Rare diseases: understanding this public health priority. 2005. [CrossRef]
6. Marwaha S, Knowles JW, Ashley EA. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. *Genome Med.* 2022;14:23. [CrossRef]
7. RARE Facts - Global Genes [Internet]. *Global Genes.* [cited: 2019 Aug 21]. [CrossRef]
8. Global Commission on Rare Disease [Internet]. [cited: 2021 Dec 6]. [CrossRef]
9. Accurate Diagnosis of Rare Diseases Remains Difficult Despite Strong Physician Interest - Global Genes [Internet]. *Global Genes.* 2014 [cited 2019 Aug 21]. [CrossRef]
10. Yan X, He S, Dong D. Determining how far an adult rare disease patient needs to travel for a definitive diagnosis: a cross-sectional examination of the 2018 National Rare Disease Survey in China. *Int J Environ Res Public Health.* 2020;17:1757. [CrossRef]
11. Molster C, Urwin D, Di Pietro L, et al. Survey of healthcare experiences of Australian adults living with rare diseases. *Orphanet J Rare Dis.* 2016;11:30. [CrossRef]
12. Heuyer T, Pavan S, Vicard C. The health and life path of rare disease patients: results of the 2015 French barometer. *Patient Relat Outcome Meas.* 2017;8:97-110. [CrossRef]
13. Miao H, Zhou J, Yang Q, et al. Long-read sequencing identified a causal structural variant in an exome-negative case and enabled preimplantation genetic diagnosis. *Hereditas.* 2018;155:32. [CrossRef]
14. Robillard JM, Feng TL, Kabacińska K. Access to genetic testing for rare diseases: existing gaps in public-facing information. *World Med Health Policy.* 2021;13:518-525. [CrossRef]
15. Erdoğan S. Integration of artificial intelligence and genome editing system for determining the treatment of genetic disorders. *Balkan Med J.* 2024;41:419-420. [CrossRef]