Opinion
Volume16:01, 2025

Human Genetics & Embryology

ISSN: 2161-0436

The Role of Whole-exome Sequencing in Diagnosing and Treating Rare Movement Disorders

Allema nn Nance*

Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45221, USA

Introduction

Movement disorders encompass a diverse group of neurological conditions that affect an individual's ability to control or coordinate voluntary movements. These disorders can range from relatively common conditions such as Parkinson's disease and essential tremor to rare and often genetically determined conditions like Huntington's disease, dystonia, and ataxia. The complexity of movement disorders, particularly those that are rare or have unusual presentations, poses a significant challenge to clinicians in terms of diagnosis and treatment. Traditionally, diagnosing these rare movement disorders relied heavily on clinical evaluation, family history, and sometimes basic genetic testing. However, the advent of high-throughput genetic sequencing technologies, particularly Whole Exome Sequencing (WES), has revolutionized the diagnostic approach to these disorders. WES enables the identification of genetic mutations that may be responsible for a patient's movement disorder, providing new avenues for diagnosis, prognosis, andtreatment strategies.

Description

Whole-exome sequencing is a cutting-edge genomic technique that allows for the sequencing of all the protein-coding regions of an individual's genome, known as the exome. The exome represents approximately 1% of the total genome but contains about 85% of known disease-causing mutations. Unlike whole-genome sequencing, which sequences the entire genetic material including non-coding regions, WES focuses on the coding portions of genes, making it a more cost-effective approach for identifying mutations linked to specific diseases. WES involves extracting DNA from a patient's blood or tissue sample, followed by the isolation and sequencing of exonic regions. The resulting data are then analyzed using sophisticated bioinformatics tools to identify any mutations that could be contributing to the patient's condition. This approach is particularly useful for diagnosing rare genetic disorders, where the causative mutations may be unknown or previously unrecognized [1].

Rare movement disorders are often difficult to diagnose because they present with a broad range of symptoms and can mimic other more common neurological conditions. Many of these disorders are caused by mutations in single genes, and in some cases, these mutations may not be detectable with standard clinical tests or panel-based genetic testing. WES has been instrumental in identifying previously unknown genetic causes of many rare movement disorders, thereby providing a more accurate and timely diagnosis. In movement disorders, the underlying genetic mutations can disrupt normal neuronal function, leading to abnormal movement patterns. For example, dystonia and ataxia are often associated with mutations in specific genes that are involved in neuronal signaling, neurotransmitter regulation, or mitochondrial function. WES can identify these mutations, even in cases where the clinical presentation is atypical or the diagnosis remains uncertain based on conventional tests [2].

For instance, mutations in the THAP1 gene have been linked to early-onset dystonia, and WES has been used to confirm these mutations in patients who present with dystonia that does not fit the typical pattern of other forms of the disease. Similarly, Spinocerebellar Ataxias (SCAs), a group of genetically heterogeneous movement disorders, can be caused by mutations in several different genes. WES helps identify these mutations, allowing for a more definitive diagnosis compared to traditional methods that may only test for the most common genetic causes. Some rare movement disorders have genetic causes that are so uncommon that they may not be included in standard diagnostic panels. WES overcomes this challenge by providing a comprehensive search of all known exonic regions for potential disease-causing mutations, even those that have never been previously linked to the disorder. This ability to uncover novel genetic mutations is particularly valuable for rare or poorly understood movement disorders. For example, neurodegeneration with brain iron accumulation (NBIA) is a rare condition that causes progressive movement abnormalities due to iron accumulation in the brain. In several cases, WES has led to the discovery of novel mutations in genes such as PANK2 and FA2H, which were previously not considered in the differential diagnosis. By identifying these mutations, WES has enabled clinicians to make an accurate diagnosis, which would have been extremely difficult using conventional methods [3].

Some rare movement disorders have genetic causes that are so uncommon that they may not be included in standard diagnostic panels. WES overcomes this challenge by providing a comprehensive search of all known exonic regions for potential disease-causing mutations, even those that have never been previously linked to the disorder. This ability to uncover novel genetic mutations is particularly valuable for rare or poorly understood movement disorders.

Neurodegeneration With Brain Iron Accumulation (NBIA) is a rare condition that causes progressive movement abnormalities due to iron accumulation in the brain. In several cases, WES has led to the discovery of novel mutations in genes such as PANK2 and FA2H, which were previously not considered in the differential diagnosis. By identifying these mutations, WES has enabled clinicians to make an accurate diagnosis, which would have been extremely difficult using conventional methods. WES not only aids in diagnosing rare movement disorders but also helps establish genotype-phenotype correlations, which can be crucial for predicting disease progression and tailoring treatment plans. For instance, the identification of a specific mutation may provide insights into the expected course of the disease, such as the age of onset, severity, and associated symptoms. In conditions like Huntington's disease, where the number of CAG repeats in the HTT gene determines the severity and age of onset, WES can be used to predict these features with a high degree of accuracy. In rare forms of early-onset Parkinson's disease, WES has revealed mutations in genes such as LRRK2 and PARK2, which can influence the disease's clinical presentation. Identifying these mutations helps clinicians understand whether the disease will have a rapid or slow progression, which is critical for determining the appropriate management and treatment strategies [4].

***Address for Correspondence:** Allemann Nance, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45221, USA, E-mail: nance.man@edu.com*

Received: 29 January, 2025, Manuscript No. hgec-25-164246; **Editor Assigned:** 31 January, 2025, PreQC No. P-164246; **Reviewed:** 14 February, 2025, QC No. Q-164246; **Revised:** 19 February, 2025, Manuscript No. R-164246; **Published:** 26 February, 2025, DOI: 10.37421/2161-0436.2025.16.273

The identification of specific genetic mutations can open the door to targeted therapies, which are designed to address the underlying genetic defect. For example, in Spinocerebellar Ataxia (SCA), gene therapy and small molecule drugs that target the genetic mutations are being explored as potential treatments. By understanding the exact genetic mutation causing the disorder, researchers can focus on developing drugs that target the molecular mechanisms involved. In Parkinson's disease, genetic discoveries have led to the development of targeted treatments aimed at specific mutations, such as those involving the LRRK2 gene. Clinical trials are currently investigating inhibitors of the LRRK2 protein as potential therapies to slow the progression of the disease in genetically predisposed patients [5].

Conclusion

Whole-exome sequencing has revolutionized the approach to diagnosing and treating rare movement disorders. By providing a comprehensive and cost-effective means of identifying genetic mutations, WES has enabled clinicians to make more accurate diagnoses, predict disease progression, and tailor treatments to the specific needs of patients. Furthermore, the insights gained from WES are paving the way for new therapeutic approaches, including gene therapies and precision medicine, which hold promise for improving the lives of individuals affected by these debilitating conditions. As WES becomes increasingly integrated into clinical practice, its potential to transform the management of rare movement disorders will only continue to grow. With ongoing research and advancements in genetic medicine, the future of diagnosing and treating rare movement disorders looks promising, offering hope for better outcomes and improved quality of life for patients.

Acknowledgment

None.

Conflict of Interest

There are no conflicts of interest by author.

References

1. Yang, Yaping, Donna M. Muzny, Jeffrey G. Reid and Matthew N. Bainbridge,et al. "Clinical whole-exome sequencing for the diagnosis of mendelian disorders." *N Engl J Med* 369 (2013): 1502-1511.

2. Marsili, Luca, Jennifer Sharma, Alberto J. Espay and Alice Migazzi, et al. "Neither a novel tau proteinopathy nor an expansion of a phenotype: reappraising clinicopathology-based nosology." *Int J Mol Sci* 22 (2021): 7292.

3. Zech, Michael and Juliane Winkelmann. "Next-generation sequencing and bioinformatics in rare movement disorders." *Nat Rev Neurol* 20 (2024): 114-126.

4. Duque, Kevin R., Luca Marsili, Andrea Sturchio and Abhimanyu Mahajan, et al. "Progressive ataxia with hemiplegic migraines: A phenotype of CACNA1A missense mutations, Not CAG repeat expansions." *The Cerebellum* 20 (2021): 134-139.

5. Tavtigian, Sean V., Marc S. Greenblatt, Steven M. Harrison and Robert L. Nussbaum, et al. "Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework." *Genet Med* 20 (2018): 1054-1060.

How to cite this article: Nance, Allemann. "The Role of Whole-exome Sequencing in Diagnosing and Treating Rare Movement Disorders." *Human Genet Embryol* 16 (2025): 273.