The genetic basis of neuromuscular diseases: What we know and what we need to discover.

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Introduction

Neuromuscular diseases (NMDs) are a diverse group of disorders that affect the peripheral nervous system, including the muscles, nerves, and neuromuscular junctions. These diseases often have a genetic basis, with mutations in specific genes leading to dysfunction in muscle and nerve function [1]. Understanding the genetic underpinnings of these diseases is crucial for diagnosis, treatment, and potential cures. This comprehensive guide explores what we know about the genetic basis of NMDs and highlights areas where further discovery is needed [2].

Identification of Disease-Causing Genes: Over the past few decades, significant progress has been made in identifying the genes responsible for various NMDs. For example: Duchenne Muscular Dystrophy (DMD): Mutations in the DMD gene, which encodes the protein dystrophin, lead to DMD. Dystrophin is crucial for maintaining muscle cell integrity, and its absence results in progressive muscle degeneration [3].

Spinal Muscular Atrophy (SMA): SMA is caused by mutations in the SMN1 gene, which is vital for the survival of motor neurons. The loss of functional SMN1 protein leads to motor neuron degeneration and muscle atrophy. Charcot-Marie-Tooth Disease (CMT): This group of inherited neuropathies is associated with mutations in over 80 different genes, including PMP22, MPZ, and GJB1, which affect myelin sheath formation and peripheral nerve function [4].

Genetic Mechanisms: The genetic mutations leading to NMDs can occur through various mechanisms: Deletions and Duplications: Large segments of DNA can be deleted or duplicated, disrupting gene function. For instance, deletions in the SMN1 gene cause SMA. Point Mutations: Single nucleotide changes can alter protein function [5]. Point mutations in the GJB1 gene cause X-linked CMT by affecting the connexin-32 protein. Splicing Mutations: Mutations affecting RNA splicing can lead to abnormal protein production. Many DMD mutations affect splicing, leading to non-functional dystrophin [6].

Inheritance Patterns: NMDs can be inherited in different ways: X-Linked Inheritance: Diseases like DMD are X-linked, meaning the mutated gene is on the X chromosome. Males are predominantly affected, while females are carriers [7]. Autosomal Dominant and Recessive Inheritance: Conditions like CMT can be inherited in both dominant and recessive manners, depending on the specific gene and mutation involved [8].

Genetic Testing and Diagnosis: Advances in genetic testing, such as next-generation sequencing (NGS), have revolutionized the diagnosis of NMDs. Whole-exome sequencing (WES) and whole-genome sequencing (WGS) can identify disease-causing mutations across the entire genome [9]. This has led to: Early and Accurate Diagnosis: Genetic testing allows for early diagnosis, even before the onset of symptoms, enabling timely interventions. Carrier Screening: Genetic testing can identify carriers of NMDs, informing family planning decisions [10].

Conclusion

The genetic basis of neuromuscular diseases is a complex and rapidly evolving field. Significant progress has been made in identifying disease-causing genes, understanding genetic mechanisms, and developing diagnostic tools. However, many challenges remain, including the identification of novel genetic causes, understanding genetic modifiers and epigenetic factors, elucidating pathophysiological mechanisms, and addressing gene-environment interactions.

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