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Neurodevelopmental phenotype of Myhre syndrome: Exploring preventive measures, the neural underpinnings, and cognitive outcomes across the lifespan

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ABSTRACT

Myhre syndrome is a rare genetic disorder caused by mutations in the SMAD4 gene, characterized by multisystemic involvement, including unique neurodevelopmental challenges. This review explores the interplay between SMAD4/TGF-beta signaling pathways and neurodevelopmental outcomes, emphasizing their implications for cognition, behavior, and brain structure. Key findings from neuroimaging studies highlight structural brain abnormalities that may underpin the cognitive and behavioral characteristics observed in affected individuals. We examine the lifespan perspective on neurodevelopment, from prenatal brain development to long-term cognitive outcomes, and discuss current therapeutic approaches, including early interventions and the potential for targeted molecular therapies. Challenges in diagnosing and monitoring neurodevelopmental symptoms in rare conditions like Myhre syndrome are highlighted, emphasizing the need for standardized assessments and regular surveillance. Additionally, this review underscores the profound psychosocial and clinical implications for patients and families, calling for integrated multidisciplinary care.

1. Introduction

Myhre syndrome is a rare autosomal dominant genetic disorder caused by pathogenic variants in the SMAD4 gene, a key mediator in the transforming growth factor-beta (TGF-β) signaling pathway. First described in 1981, Myhre syndrome is characterized by a constellation of features, including short stature, craniofacial abnormalities, skeletal anomalies, and progressive fibrosis of soft tissues [1]. While much is known about the physical manifestations of this condition, the neurodevelopmental phenotype remains underexplored. Understanding the cognitive, behavioral, and neurological aspects of Myhre syndrome is critical for comprehensive patient care, as these features significantly impact quality of life and long-term outcomes.

The TGF-β pathway, implicated in Myhre syndrome, plays a fundamental role in brain development, neuroplasticity, and synaptic signaling [2]. Dysregulation of this pathway has been associated with a range of neurodevelopmental disorders, suggesting potential parallels in the neurological sequelae of Myhre syndrome. Case reports and small-scale studies have documented intellectual disability, autism spectrum traits, and speech and motor delays in affected individuals [3]. However, these findings are scattered across isolated reports, limiting our ability to draw cohesive conclusions about the syndrome's neurodevelopmental impact. Figure 1 summarizes the SMAD4/TGF-β pathway's normal neurodevelopmental functions and the neurodevelopmental impacts of its dysregulation in Myhre syndrome.

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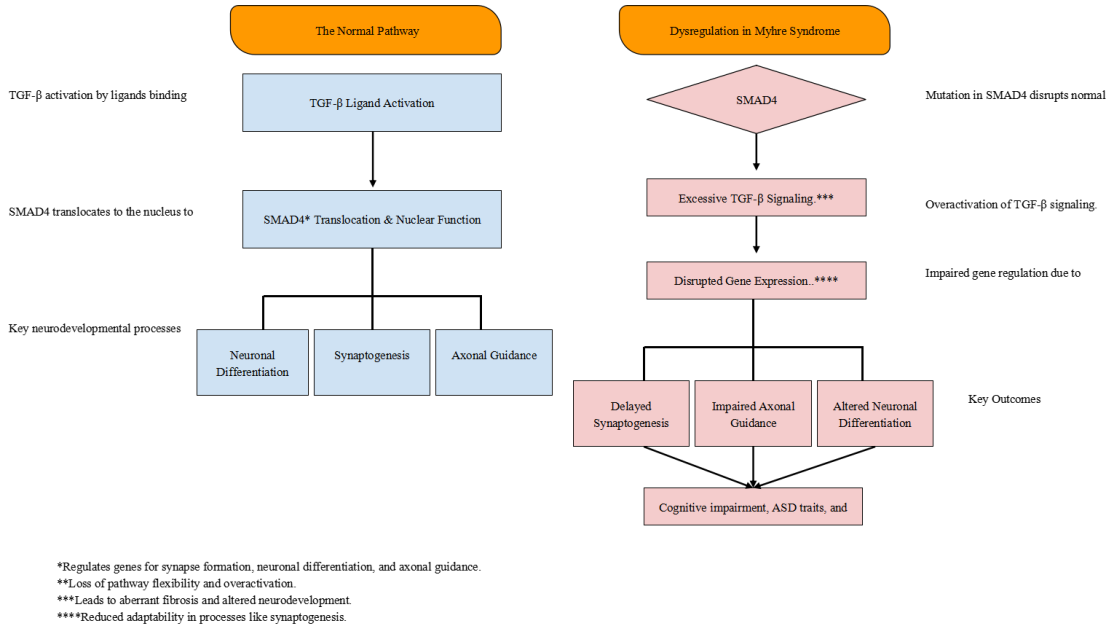

Fig. 1 - Flowchart representing the roles of the SMAD4/TGF-β signaling pathway in normal neurodevelopment, highlighting its regulation of neuronal differentiation, synaptogenesis, and axonal guidance, and illustrating the impacts of pathway dysregulation in Myhre syndrome, including cognitive and behavioral consequences.

2. Overview of Myhre Syndrome

Myhre syndrome is a rare genetic disorder with a diverse range of clinical manifestations affecting multiple organ systems. The condition arises from heterozygous mutations in the SMAD4 gene, which encodes a critical mediator of the transforming growth factor-beta (TGF-β) signaling pathway [4]. This pathway regulates cell proliferation, differentiation, and extracellular matrix production, processes that are essential for normal growth and development. Pathogenic mutations in SMAD4 lead to dysregulated signaling, which manifests as progressive fibrosis, short stature, distinctive craniofacial features, joint stiffness, and cardiovascular complications [5]. The systemic nature of Myhre syndrome is evident in its impacts across multiple organ systems, as summarized in Table 1.

Table 1- Key Clinical Features of Myhre Syndrome Across Organ Systems

Organ System	Key Features	Notes
Skeletal	Joint stiffness, contractures, short stature, and limited joint mobility	Progressive stiffness often noted in early childhood; can impair daily function.
Cardiovascular	Congenital heart defects, aortic root dilation, hypertension	Life-threatening complications may require surveillance and early intervention.
Respiratory	Restrictive lung disease, recurrent respiratory infections, and tracheal stenosis	Chronic respiratory insufficiency can occur, necessitating tailored respiratory care.
Neurological	Developmental delay, intellectual disability, behavioral challenges, and neurodevelopmental deficits	Cognitive profiles vary; attention to behavioral therapies is critical for management.
Endocrine	Delayed puberty, hypothyroidism, and growth hormone abnormalities	Endocrine monitoring is important for addressing growth and pubertal concerns.
Craniofacial	Midface hypoplasia, small mouth, prognathism, and thickened skin	Characteristic facial features assist in clinical diagnosis.
Dermatological	Hyperpigmented skin, thickened dermis, and keloid formation	Dermatological findings may lead to cosmetic and functional concerns
Gastrointestinal	Feeding difficulties, constipation, and abdominal pain	GI symptoms can impact nutrition and quality of life.
Reproductive	Infertility and impaired gonadal development	Counseling for reproductive health is often necessary.
Hematological	Increased risk of thromboembolism and bleeding abnormalities	Comprehensive management strategies are required to address coagulation issues.

The clinical presentation of Myhre syndrome evolves over time, with many features becoming more pronounced with age. Early childhood symptoms often include growth delays, developmental delays, and recurrent respiratory issues. As patients grow older, additional complications such as joint contractures, restrictive pulmonary disease, and cardiac anomalies may develop, significantly impacting quality of life [6]. Despite advancements in genetic testing and molecular diagnostics, the syndrome's rarity presents challenges in early diagnosis and comprehensive care.

3. SMAD4 and Neurodevelopmental Pathways

The SMAD4 gene plays a pivotal role in the TGF-β signaling pathway, which regulates a wide range of cellular processes critical to neurodevelopment, including cell differentiation, proliferation, apoptosis, and synaptic plasticity [7]. This pathway's activity is particularly vital during early brain development, where it influences neural tube formation, cortical layering, and axonal guidance. In individuals with Myhre syndrome, mutations in SMAD4 disrupt these processes, leading to structural and functional abnormalities in the central nervous system [8].

Research suggests that dysregulated TGF-β signaling in Myhre syndrome may contribute to altered neurogenesis and excessive fibrosis in brain tissues, which can impair neuronal communication and plasticity [9]. These disruptions are associated with a variety of neurodevelopmental challenges, including intellectual disabilities, autism spectrum disorders, and behavioral abnormalities. Animal models with SMAD4 mutations have provided valuable insights into the molecular mechanisms underlying these deficits, revealing reduced synaptic connectivity and changes in the expression of genes involved in synaptic organization and neurotransmission [10].

In addition to structural abnormalities, there is emerging evidence that aberrant TGF-β signaling can impact functional neural networks, contributing to impairments in executive functioning, attention, and social cognition observed in Myhre syndrome [11]. Understanding the link between SMAD4 mutations and these neurodevelopmental pathways not only highlights the importance of the TGF-β pathway in brain function but also provides potential targets for therapeutic interventions aimed at mitigating cognitive and behavioral symptoms. Further studies are essential to elucidate the precise mechanisms and identify strategies to promote neural resilience in affected individuals. The relationship between SMAD4 mutations, disrupted TGF-β signaling, and their downstream impacts on neurodevelopmental pathways is illustrated in Figure 2.

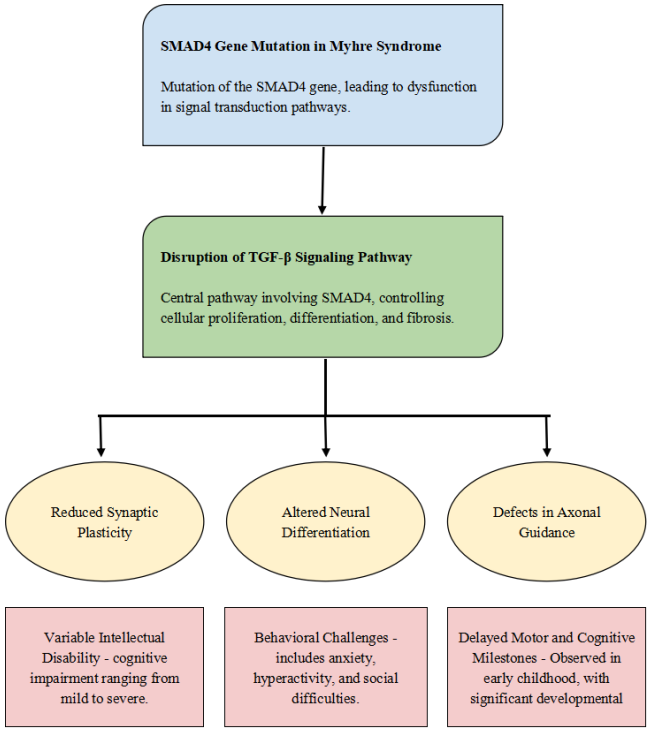

Fig. 2 - SMAD4 and Neurodevelopmental Pathways

4. Cognitive and Behavioral Characteristics

Individuals with Myhre syndrome often exhibit a spectrum of cognitive and behavioral features that vary widely in severity, reflecting the complex interplay between genetic mutations, neurodevelopmental disruptions, and environmental factors [12]. Intellectual disability is a frequent finding, with most individuals demonstrating mild to moderate impairments. These challenges often manifest as delays in language acquisition, reduced problem-solving skills, and difficulties with adaptive functioning, which impact daily living and educational attainment [13].

Behaviorally, Myhre syndrome is frequently associated with features of autism spectrum disorder (ASD), including repetitive behaviors, restricted interests, and challenges with social interactions. These behaviors can stem from both structural brain abnormalities and the disrupted neural pathways associated with SMAD4 mutations. In addition, attention-deficit/hyperactivity disorder (ADHD) symptoms, such as impulsivity, hyperactivity, and inattention, are commonly reported, further complicating the clinical profile [14].

Beyond the neurodevelopmental traits, emotional dysregulation, including heightened anxiety, mood instability, and sensory sensitivities, is prevalent among individuals with Myhre syndrome [14]. These behavioral characteristics can be exacerbated by the physical and social challenges associated with the condition, underscoring the importance of a multidisciplinary approach to care. Tailored interventions, such as cognitive-behavioral therapy and structured educational supports, have shown promise in addressing these challenges and improving quality of life [15].

5. Lifespan Perspective on Neurodevelopment

Neurodevelopment in individuals with Myhre syndrome exhibits distinct characteristics at various stages of life, beginning as early as the fetal and neonatal periods. Prenatal imaging studies have occasionally identified abnormalities such as ventriculomegaly or delayed cortical development, which may indicate early disruptions in brain formation [16]. In the neonatal stage, complications such as poor feeding, hypotonia, or seizures can emerge, further highlighting the vulnerability of the developing nervous system in this syndrome [17]. These early findings underline the importance of monitoring brain development during the critical prenatal and perinatal windows.

During childhood, neurodevelopmental challenges become more apparent, often manifesting as delayed achievement of motor and cognitive milestones, learning difficulties, and speech impairments [18]. Behavioral issues, including social communication deficits and features overlapping with autism spectrum disorder, have also been noted [19]. Early intervention programs focusing on physical, occupational, and speech therapies have demonstrated benefits in mitigating some developmental delays [20]. Despite these interventions, the variability in cognitive and behavioral outcomes presents a significant challenge for families and caregivers.

In adulthood, individuals with Myhre syndrome often face persistent cognitive challenges, though the extent of these difficulties varies widely. Longitudinal studies suggest that some adults achieve a degree of independence in daily living, while others require ongoing support for managing complex tasks [14]. Behavioral and psychiatric comorbidities, such as anxiety or obsessive-compulsive tendencies, may also emerge or intensify in later years, further complicating management [14]. Understanding the trajectory of neurodevelopment across the lifespan provides critical insights into the comprehensive care needs of individuals with Myhre syndrome, emphasizing the importance of a multidisciplinary approach to improve quality of life.

6. Therapeutic Approaches and Interventions

The management of neurodevelopmental symptoms in individuals with Myhre syndrome typically involves a combination of targeted therapies designed to address specific cognitive, behavioral, and developmental challenges. Early intervention programs play a crucial role in mitigating delays, with tailored strategies such as speech therapy, occupational therapy, and physical therapy to support communication, motor skills, and social engagement [14]. Cognitive-behavioral therapy (CBT) has shown promise in managing behavioral symptoms such as anxiety or obsessive-compulsive tendencies, while individualized educational programs can accommodate learning difficulties in academic settings [21]. These approaches underscore the importance of a multidisciplinary care team that collaborates closely with families to address the diverse needs of each individual.

Emerging research suggests potential avenues for future therapeutic interventions targeting the underlying molecular mechanisms of Myhre syndrome. Given the central role of SMAD4 in the TGF-beta signaling pathway, therapies aimed at modulating this pathway could hold promise for addressing some of the systemic and neurodevelopmental manifestations of the syndrome [22]. Preclinical studies exploring pathway inhibitors and other molecular targets have shown encouraging results in animal models, offering hope for translation into clinical trials [22]. Additionally, advances in neuroplasticity-based interventions, such as transcranial magnetic stimulation or cognitive training programs, may provide novel ways to enhance cognitive function and adaptability in affected individuals [23].

While these developments are promising, significant challenges remain, particularly in ensuring the safety and efficacy of experimental therapies in a rare disease population. Continued investment in research and collaboration among specialists, patients, and advocacy groups will be essential for advancing therapeutic options and improving outcomes for individuals with Myhre syndrome.

7. Challenges in Diagnosis and Surveillance

Diagnosing neurodevelopmental issues in rare disorders such as Myhre syndrome presents unique challenges due to the heterogeneity of symptoms and the limited availability of clinical expertise. Many neurodevelopmental features, such as developmental delays, learning disabilities, or behavioral abnormalities, overlap significantly with more common conditions like autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD), leading to potential misdiagnoses or delayed recognition. Additionally, the rarity of Myhre syndrome means that clinicians may lack familiarity with its full spectrum of manifestations, including the specific neurodevelopmental patterns associated with SMAD4 mutations. As a result, early identification of neurodevelopmental complications often depends on heightened clinical awareness and multidisciplinary evaluations [24].

To improve outcomes, there is a critical need for standardized assessments and regular surveillance tailored to the unique needs of individuals with Myhre syndrome. Comprehensive neurodevelopmental evaluations, encompassing cognitive, motor, language, and behavioral domains, can provide a clearer picture of the individual's strengths and challenges [25]. Standardized tools for monitoring progress, combined with consistent follow-ups, are essential for identifying emerging issues and adjusting therapeutic plans accordingly. Moreover, genetic counseling and the integration of molecular diagnostics into clinical care can aid in confirming the diagnosis and guiding management strategies [26]. By addressing these diagnostic and surveillance challenges, healthcare providers can better support individuals with Myhre syndrome in reaching their developmental potential. Diagnosing and monitoring neurodevelopmental features in Myhre syndrome presents unique challenges due to its rarity and complexity. A systematic approach is essential, beginning with clinical recognition and followed by multidisciplinary evaluation, genetic confirmation, and ongoing surveillance. Figure 3 illustrates this process, highlighting the sequential and parallel steps involved in identifying and managing neurodevelopmental outcomes. By visualizing these steps, the

flowchart underscores the importance of regular reassessments and personalized management plans to address evolving patient needs.

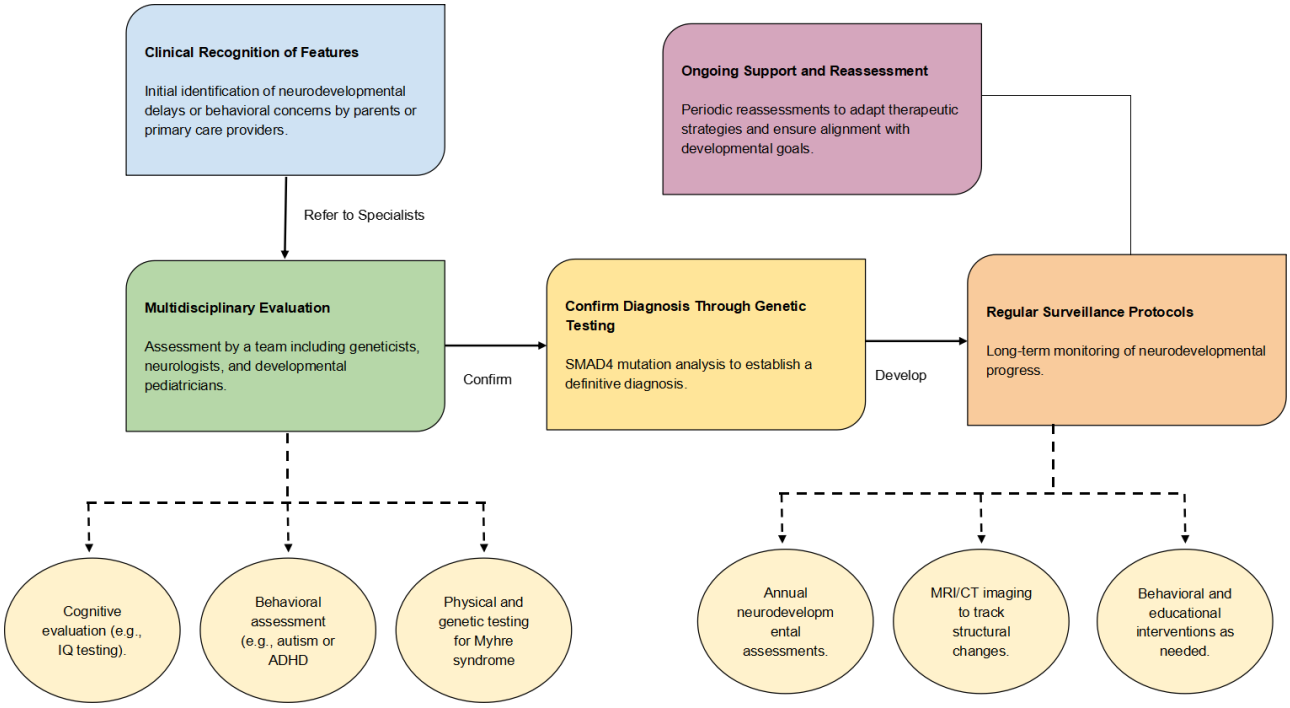

Fig. 3 - Diagnostic and Surveillance Process for Neurodevelopmental Features in Myhre Syndrome

8. Implications for Patients and Families

Living with a rare condition brings unique emotional and practical challenges for patients and their families [27][28]. Parents often face uncertainty during the diagnostic journey, with prolonged periods of misdiagnosis or lack of clarity about their child's condition [29]. Upon receiving a diagnosis, they may experience mixed emotions, including relief at having an explanation and anxiety about the future. Families must also adapt to the realities of managing neurodevelopmental symptoms, which often involve behavioral difficulties, learning disabilities, or cognitive delays. Practical challenges, such as navigating healthcare systems, coordinating therapies, and accessing educational resources, can place significant strain on caregivers [30].

Support networks, including family, community groups, and organizations like the Myhre Syndrome Foundation, play a pivotal role in improving quality of life. These networks provide emotional support, foster community connection, and facilitate access to valuable resources, such as educational materials and specialist recommendations [31]. Patient education is also crucial, equipping families with the knowledge needed to advocate effectively for tailored care plans. Programs designed to enhance coping strategies for caregivers and empower them in decision-making processes are essential components of holistic care.

Looking ahead, continued advancements in research and clinical care offer hope for improved outcomes. Initiatives focusing on patient advocacy, awareness, and inclusion of family perspectives in clinical studies are key to shaping future care strategies. Families benefit from being actively involved in research that emphasizes patient-reported outcomes and long-term follow-up data [32]. Empowering patients and caregivers with clear, accessible information about therapeutic options, prognosis, and ongoing developments in the field fosters a sense of agency and optimism.

Table 2 - shows options regarding resources and support for families with Myhre syndrome

Category	Examples
Support Organizations	Myhre Syndrome Foundation, Rare Disease Network, Genetic Counseling Services
Therapeutic Resources	Cognitive-behavioral therapy, Special education programs, Early intervention services
Community Support	Online forums, Local support groups, Social media communities
Educational Materials	Guides on neurodevelopment, Caregiver coping strategies, Advocacy toolkits

9. Preventive Medicine Framework: Early Identification, Risk Stratification, and Neurodevelopmental Surveillance in Myhre Syndrome

From a preventive medicine perspective, Myhre syndrome represents a paradigm in which genetically mediated neurodevelopmental risk is identifiable early but remains inconsistently addressed through structured prevention strategies. Although the condition is rare, its predictable molecular etiology and multisystem trajectory allow for the application of prevention principles aimed at minimizing downstream cognitive, behavioral, and psychosocial morbidity.

9.1 Primary Prevention: Genetic Counseling and Reproductive Risk Awareness

While primary prevention in monogenic disorders is inherently limited, genetic counseling plays a central preventive role in Myhre syndrome. Identification of pathogenic SMAD4 variants enables informed reproductive decision-making, anticipatory guidance, and early planning for developmental surveillance. Counseling also provides an opportunity to

address modifiable environmental and psychosocial factors—such as early access to developmental services—that may influence neurodevelopmental outcomes despite an immutable genetic risk.

9.2 Secondary Prevention: Early Neurodevelopmental Screening and Structured Surveillance

Secondary prevention is where the greatest opportunity for impact exists. Given evidence that neurodevelopmental manifestations emerge early and progress across childhood, systematic screening for cognitive, language, motor, and behavioral delays should be initiated in infancy and repeated longitudinally. Incorporating standardized neurodevelopmental assessments into routine care allows for earlier identification of emerging deficits before they translate into entrenched functional impairments.

Neuroimaging findings and known disruptions in SMAD4/TGF-β signaling further support the need for risk-stratified surveillance, particularly during critical neurodevelopmental windows. Preventive frameworks emphasizing scheduled reassessment—rather than symptom-triggered evaluation—align with broader preventive medicine principles used in other high-risk pediatric populations.

9.3 Tertiary Prevention: Mitigating Long-Term Cognitive and Psychosocial Burden

Tertiary prevention focuses on reducing disability and optimizing functional outcomes once neurodevelopmental impairments are established. Early and sustained intervention through speech, occupational, behavioral, and educational therapies can attenuate secondary consequences such as academic failure, social isolation, caregiver burden, and mental health comorbidities. From a public health standpoint, these interventions reduce long-term healthcare utilization and improve participation in education and community life.

Importantly, preventive strategies must extend beyond the individual to include family-centered interventions, caregiver education, and system-level coordination of services. These approaches align with preventive medicine's emphasis on minimizing cumulative morbidity across the lifespan rather than solely treating established deficits.

Population Health Relevance of Rare Neurodevelopmental Disorders

Although Myhre syndrome is rare, it exemplifies a broader preventive challenge in genetic neurodevelopmental disorders: how early molecular diagnosis can be translated into proactive, standardized preventive care. Lessons from Myhre syndrome are therefore generalizable to other SMAD4-related and TGF-β–mediated conditions, reinforcing the relevance of this framework within preventive medicine.

Integrating neurodevelopmental surveillance into rare disease care pathways highlights the importance of prevention-focused models that prioritize early identification, longitudinal monitoring, and anticipatory intervention—core principles of preventive medicine that remain underutilized in rare genetic disorders.

10. Conclusion and Future Directions

This paper provides a comprehensive overview of the neurodevelopmental aspects of Myhre syndrome, emphasizing the pivotal role of SMAD4 in influencing brain development and cognitive outcomes. By integrating findings from structural brain imaging, cognitive assessments, and behavioral studies, we highlight the profound interplay between molecular pathways, neuroanatomy, and neurodevelopmental phenotypes in this rare disorder. These insights underscore the importance of early diagnosis, individualized therapeutic approaches, and multidisciplinary care to address the unique challenges faced by patients with Myhre syndrome and their families.

While this review aggregates valuable information, several limitations must be acknowledged. First, the rarity of Myhre syndrome limits the availability of large-scale, longitudinal studies, making it difficult to generalize findings across diverse populations. Many existing studies rely on single-case reports or small cohorts, which, while insightful, do not provide a comprehensive picture of neurodevelopmental trajectories. Additionally, this paper does not explore in depth the potential for emerging therapies, such as gene editing or SMAD4-targeted treatments, which remain in their infancy. Future research should prioritize collaborative multicenter studies to establish standardized assessments, evaluate long-term outcomes, and explore novel therapeutic interventions.

Moving forward, a collaborative approach is essential to advance understanding and care for individuals with Myhre syndrome. Researchers, clinicians, and patient advocacy groups must work together to conduct robust studies on SMAD4's role in neurodevelopment, investigate therapeutic innovations, and develop family-centered care strategies. The integration of patient and caregiver perspectives in research design will ensure that scientific advancements translate into meaningful clinical benefits. With sustained focus and collaboration, the field has the potential to significantly improve the quality of life for individuals with Myhre syndrome and their families.

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