

Mucopolysaccharidosis Type II (Hunter Syndrome): A Brief Review of Pathophysiology, Clinical Spectrum, and Current Therapeutic Strategies

✉ Havva Yazıcı

Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism, İzmir, Türkiye

Abstract

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is a rare, X-linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase, resulting in progressive accumulation of heparan sulfate and dermatan sulfate in multiple tissues. The disease presents as a broad clinical spectrum ranging from attenuated forms with preserved cognitive function to severe neuronopathic forms characterized by progressive neurodegeneration. Common clinical manifestations include coarse facial features, hepatosplenomegaly, skeletal abnormalities, cardiac valve disease, airway obstruction, hearing loss, and neurological impairment. The diagnosis is established by demonstrating deficient enzyme activity and by molecular confirmation of pathogenic variants in the *IDS* gene. Intravenous enzyme replacement therapy has significantly improved somatic manifestations and the quality of life; however, its inability to cross the blood–brain barrier limits its effectiveness in preventing neurological disease progression. Recent advances, including hematopoietic stem cell transplantation, blood–brain barrier-penetrating enzyme replacement therapies, intrathecal and intracerebroventricular enzyme administration, and gene therapy, offer promising approaches to address central nervous system involvement. This review summarizes the current understanding of the pathophysiology, clinical spectrum, diagnosis, and evolving therapeutic strategies for MPS II, with particular emphasis on emerging treatments targeting neurological disease.

Keywords: Mucopolysaccharidosis type II; Hunter syndrome; Lysosomal storage disorder; Enzyme replacement therapy; Gene therapy; Newborn screening

INTRODUCTION

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is a rare, X-linked recessive, multisystemic, and progressive lysosomal storage disorder.¹ The disease was first described in 1917 by Canadian physician Charles A. Hunter in two male siblings. Hunter characterized them as having severe somatic manifestations, including macrocephaly, dysmorphic facial features, hepatosplenomegaly, joint contractures, hearing impairment, noisy breathing, and cardiomegaly, despite having normal intelligence. The term mucopolysaccharidosis was introduced by Brante in 1952, and the biochemical basis of the disease was established in 1968 when Fratantoni et al. described the *in vitro* phenomenon of cross-correction, demonstrating that

enzyme-deficient cells could be functionally corrected by enzyme-producing cells.² The core biochemical defect is a deficiency of the enzyme iduronate-2- sulfatase (I2S) (EC 3.1.6.13), which plays a vital role in the lysosomal catabolism of glycosaminoglycans (GAGs). Specifically, I2S catalyzes the hydrolysis of the C-2 sulfate ester bond at the non-reducing terminal L-iduronic acid residues of dermatan sulfate (DS) and heparan sulfate (HS). The reduction or complete absence of I2S activity leads to the massive, progressive accumulation of partially degraded HS and DS within the lysosomes of virtually every cell type in the body, as well as within the extracellular matrix.²

Although the progressive lysosomal accumulation of HS and DS is the primary biochemical hallmark of MPS II, the



Address for Correspondence: Havva Yazıcı, MD, Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism, İzmir, Türkiye

E-mail: havvaya@gmail.com **ORCID ID:** orcid.org/0000-0002-2564-7420

Received: 04.07.2026 **Accepted:** 09.09.2026 **Publication Date:** 30.09.2026

Cite this article as: Yazıcı H. Mucopolysaccharidosis type II (Hunter syndrome): a brief review of pathophysiology, clinical spectrum, and current therapeutic strategies. *Inherit Metab Disord Nutr.* 2026;2:25–30



Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of Child Nutrition Metabolism Association. This is an open access article under the Creative Commons AttributionNonCommercial 4.0 International (CC BY-NC 4.0) License.

pathological consequences of this storage process extend considerably beyond simple substrate deposition.³ Increasing evidence suggests that GAG accumulation initiates a complex network of secondary cellular disturbances, including lysosomal dysfunction, impaired autophagy, oxidative stress, and chronic inflammation, which collectively drive tissue injury and multisystem disease progression. The pathophysiology extends far beyond the mere mechanical engorgement of cells by HS and DS, encompassing a destructive cascade of cellular dysfunction and inflammatory signaling. Primary GAG accumulation impairs lysosomal function, thereby inhibiting other acid hydrolases and leading to secondary lysosomal accumulation of neurotoxic and pro-inflammatory molecules, including GM2 and GM3 gangliosides, globotriaosylsphingosine, unesterified cholesterol, and tau proteins.⁴ Furthermore, undegraded HS fragments structurally mimic the lipopolysaccharides of Gram-negative bacteria and act as potent ligands for toll-like receptor 4 (TLR4) on the surface of microglia and peripheral macrophages. Activation of the TLR4-MyD88 pathway induces NF- κ B signaling and activates the NLRP3 inflammasome, leading to excessive release of pro-inflammatory mediators, including cytokines such as interleukin-1 β and tumor necrosis factor- α , and matrix metalloproteinases, thereby promoting chronic systemic inflammation and neurodegeneration. In parallel, the massive intracellular GAG burden compromises lysosomal membrane integrity, allowing destructive hydrolases, such as cathepsin B, to leak into the cytosol and accelerate cell death. Simultaneously, disruption of autophagic and mitophagic flux markedly increases intracellular oxidative stress, further exacerbating cellular dysfunction and tissue damage.⁵

This enzyme is encoded by the *IDS* gene, linking the biochemical defect directly to the disease's underlying genetic cause. MPS II is caused by pathogenic variants in the *IDS* gene located at Xq28 on the X chromosome. The *IDS* gene spans approximately 24 kb, contains nine exons, and encodes a 550-amino acid polypeptide.⁶ To date, over 800 distinct pathogenic variants have been identified, including nonsense and missense mutations, splice-site mutations, and major structural alterations. A significant challenge in understanding the genetic architecture is the presence of the IDSP1 pseudogene, located approximately 20–25 kb telomeric to the active *IDS* gene. Sharing up to 100% sequence homology with specific exons of the *IDS* gene, this pseudogene predisposes the locus to unequal homologous recombination events. These events frequently result in complex genetic rearrangements, such as inversions and large deletions, which are characteristically associated with severe disease phenotypes. Although MPS II almost exclusively affects males due to its X-linked recessive inheritance, rare symptomatic female cases have been documented, primarily resulting from skewed X-chromosome inactivation or structural chromosomal abnormalities.^{3,7}

Reflecting these underlying genetic drivers, the epidemiological landscape of MPS II demonstrates significant global variation.^{7,8} Worldwide, it is recognized as an ultra-rare lysosomal storage disorder, with a reported birth prevalence ranging from 0.13 to 2.16 per 100,000 live births.⁹ Striking geographic heterogeneity and ethnicity-driven variations are documented worldwide.^{8,10} In East Asian populations—such as Taiwan (1.07/100,000), Japan (0.84/100,000), and South Korea (0.74/100,000)—MPS II represents the predominant subtype, accounting for 50% to 55% of all diagnosed MPS cases.^{11–13} This high relative frequency is primarily driven by founder variants, particularly by high allele frequencies of p.R468 alterations and by recurrent IDS–IDSP1 genomic recombinations.^{14,15} Conversely, MPS II represents only 4% to 27% of all MPS diagnoses in European and North American populations, with birth prevalence reported as 0.13 per 100,000 in Norway, 0.64 per 100,000 in Germany, and 0.26 per 100,000 in the United States.^{12,16} Real-world data from high-throughput newborn screening (NBS) panels indicate that traditional clinical ascertainment has underestimated disease incidence; for example, US screening initiatives revealed a prevalence of 1 in 73,290, higher than historical registry estimates.¹⁷ Owing to its X-linked recessive inheritance pattern, MPS II almost exclusively affects hemizygous males and has a male-specific birth prevalence ranging from 2.05 per 100,000 male live births in Taiwan to 4.2 per 100,000 male live births in Estonia.^{11,18} Symptomatic cases in females remain extraordinarily rare, with approximately 24 confirmed cases documented in the global literature. Disease expression in females requires a total loss of functional enzyme activity, which predominantly arises from extremely skewed X-chromosome inactivation (silencing the normal allele), structural X-chromosome rearrangements (e.g., monosomy X/Turner syndrome or X-autosome translocations), or exceptionally rare homozygous inheritance resulting from parental consanguinity.⁹

CLINICAL FINDINGS

MPS II presents as a continuous phenotypic spectrum, driven by the progressive accumulation of GAGs at the cellular and tissue levels. Clinically, the disease is categorized into two main phenotypes based on the presence of neurological involvement and the rate of progression: the severe (neuronopathic) and the attenuated (non-neuronopathic) phenotypes. The neuronopathic form, representing approximately two-thirds of the patient population, typically manifests between 18 and 36 months of age. The severe phenotype is dominated by progressive cognitive and neurobehavioral decline. Conversely, patients with the attenuated form do not experience significant cognitive regression and often survive into adulthood.¹⁹ However, data from the Hunter Outcome Survey (HOS), the largest global registry for patients with MPS II, strongly indicate that patients with the attenuated form experience a somatic disease burden as severe

as that of their neuronopathic counterparts and require frequent surgical interventions for manifestations such as hernias and carpal tunnel syndrome during the first two decades of life.²⁰ The clinical features of the severe and attenuated phenotypes of MPS II are summarized in Table 1.

The clinical distinction among phenotypic forms is most evident in the extent of neurological involvement, the principal determinant of disease severity and long-term prognosis. Primary neurological involvement is the hallmark of the severe phenotype, presenting as developmental arrest followed by regression, typically beginning at 18–36 months.⁷ Elevated levels of neurofilament light chain in cerebrospinal fluid (CSF) and serum have recently been established as robust biomarkers of progressive axonal damage and neurodegeneration. Clinically, this manifests as extreme hyperactivity, aggression, sleep disturbances, and ultimately intractable seizures. Secondary neurological complications arise from GAG deposition in the meninges and neural vasculature, leading to communicating hydrocephalus, cervical spinal stenosis (cervical myelopathy), and carpal tunnel syndrome.²¹

Skeletal dysplasia is largely driven by the accumulation of DS. DS interferes with small leucine-rich proteoglycans, disrupting collagen fibril assembly in the extracellular matrix. Furthermore, accumulated HS competitively inhibits the signaling pathways of fibroblast growth factor and bone morphogenetic protein, both of which are critical for bone morphogenesis. Patients develop restricted joint mobility, claw-hand deformities, short stature, kyphoscoliosis, thickened ribs, and the characteristic skeletal presentation, dysostosis multiplex.³

DS is a major component of normal cardiac valves. In MPS II, massive DS deposition within valve leaflets and the myocardium triggers fibrosis and inflammation, leading to severe valvular disease, particularly mitral and aortic regurgitation or stenosis. Left ventricular hypertrophy,

arrhythmias, and eventual heart failure follow and together constitute one of the leading causes of mortality.^{3,22}

GAG deposition in mucosal tissue causes macroglossia, adenotonsillar hypertrophy, and vocal cord thickening. More critically, tracheobronchomalacia, combined with highly viscous secretions, drastically narrows the upper and lower airways. This leads to progressive obstructive sleep apnea, noisy breathing, difficult intubation, and life-threatening recurrent respiratory infections. Mixed conductive and sensorineural hearing loss is nearly universal, resulting from chronic otitis media, ossicular dysostosis, and cochlear nerve compression.⁷

GAG storage in the reticuloendothelial system results in almost universal hepatosplenomegaly and associated inguinal or umbilical hernias. Pebble-like, ivory-colored skin lesions on the back and upper arms have been reported in MPS II. Notably, unlike MPS I or VI, significant corneal clouding is extremely rare in MPS II.²³ This is hypothesized to result from the protective effect of an extra sulfate group on the DS molecules that accumulate in MPS II.²⁴

DIAGNOSIS

Establishing a prompt and precise diagnosis of MPS II requires an integrated approach that combines clinical awareness with targeted biochemical screening, enzymatic confirmation, and molecular characterization.²³ Initial diagnostic evaluation is commonly prompted by overt physical features or an abnormal NBS result. Quantitative assessment of total urinary GAGs (uGAGs) via dye-binding assays offers a useful initial indicator; however, it lacks specificity and may yield false-negative results. To avoid false negatives, qualitative GAG profiling by liquid chromatography–tandem mass spectrometry or urine GAG electrophoresis is preferred for specifically detecting elevated levels of DS and HS.^{15,25}

In male patients, definitive biochemical diagnosis relies on demonstrating deficient or completely absent I2S activity in

Table 1. Clinical features of the severe and attenuated phenotypes in mucopolysaccharidosis type II.		
Clinical feature/system	Neuronopathic (severe) phenotype	Attenuated phenotype
Prevalence and onset	2/3 of cases; typical onset at 18–36 months	1/3 of cases; typically later onset
Primary CNS disease	Progressive cognitive decline, developmental arrest, hyperactivity, aggression, and intractable seizures	Absent or minimal; preserved cognitive functions and normal neurodevelopmental trajectory
Secondary CNS disease	Communicating hydrocephalus, cervical spinal stenosis, and carpal tunnel syndrome	High risk for hydrocephalus, spinal stenosis, and carpal tunnel syndrome (similar to severe form)
Somatic burden	Severe: Dysostosis multiplex, restricted joint mobility, valvular heart disease, macroglossia, and upper airway obstruction	Marked somatic burden; early surgical interventions are frequently required for hernias and carpal tunnel syndrome
Prognosis	Shortened survival; premature death is typically driven by neurodegeneration and cardiorespiratory failure	Prolonged survival into adulthood; prognosis depends on somatic and valvular complications
CNS, central nervous system.		

leukocytes, plasma, or cultured fibroblasts. Dried blood spot enzyme assays have revolutionized early detection by providing a rapid, minimal-volume substrate suitable for both high-throughput NBS and primary diagnostic triage. Notably, it is clinically mandatory to measure the normal activity of at least one other sulfatase to rule out multiple sulfatase deficiency.¹⁵

Identifying pathogenic variants in the *IDS* gene provides essential genetic confirmation, enables genotype–phenotype predictions, and guides family counseling. Standard Sanger sequencing or targeted next-generation sequencing (NGS) panels effectively detect single- nucleotide variants and small insertions or deletions. Nonetheless, molecular confirmation is often complicated by IDS_{P1}, a *pseudogene* located ~20–25 kb telomeric to IDS and sharing *extensive* sequence identity with IDS. Non-allelic homologous recombination between these loci accounts for 10–15% of pathogenic alleles, producing complex inversions and structural deletions that can easily escape detection by conventional Polymerase Chain Reaction (PCR) or short-read NGS. Resolving these complex genomic rearrangements often requires dedicated techniques such as long-read sequencing, MLPA, or PCR-RFLP analysis.^{14,23,26}

Detection of female carriers is a critical component of genetic counseling, as MPS II is inherited in an X-linked recessive pattern in which approximately 92% of mothers of affected males are carriers and ~8% carry *de novo* mutations.²⁷ Measurement of I2S enzyme activity or uGAGs in females is clinically unreliable for carrier identification because random X-chromosome inactivation causes significant overlap with normal control ranges. Although most carriers are clinically asymptomatic, skewed X-chromosome inactivation can occasionally result in mild, progressive somatic manifestations—such as joint stiffness, carpal tunnel syndrome, hypoacusia, and skeletal anomalies—warranting longitudinal clinical monitoring.²⁸ Consequently, targeted molecular genetic testing for the familial IDS variant is the only reliable approach to identify female carriers.¹⁵ Once the proband's mutation is established, direct DNA-based methodologies—including Sanger sequencing, restriction fragment digestion, specialized PCR assays for gene–pseudogene recombinations, and high-sensitivity NGS, capable of detecting low-level somatic or germline mosaicism—enable precise cascade testing of at-risk female relatives and provide essential options for prenatal and preimplantation genetic diagnosis.^{14,23,25}

CURRENT TREATMENTS

The therapeutic management of MPS II has historically shifted from palliative, symptom-focused care to disease-specific therapy.²⁰ Although current treatments significantly alter the somatic course of the disease, addressing the profound neurological burden remains a critical challenge.

Intravenous (IV) administration of recombinant human I2S is the current first-line treatment for MPS II. When administered weekly at a dose of 0.5 mg/kg, IV enzyme replacement therapy (ERT) effectively targets somatic macrophages via mannose-6-phosphate receptor-mediated endocytosis. Clinical trials and extensive real-world registry data, including findings from the HOS, consistently show that ERT rapidly reduces uGAG excretion and normalizes liver and spleen volumes. It also provides measurable improvements or stabilization in functional endurance [e.g., the 6-minute walk test (6MWT)] and pulmonary capacity.²⁰ While IV ERT effectively manages systemic disease, its inability to penetrate avascular tissues (such as cardiac valves and cartilage) and the central nervous system limits its overall therapeutic efficacy.²⁹ In addition, avascular or poorly vascularized tissues, such as cardiac valves, bone growth plates, and cartilage, exhibit poor enzyme penetration. Consequently, valvulopathy, airway obstruction, and skeletal dysplasia often continue to progress despite long-term enzymatic treatment.³⁰ Another important therapeutic limitation is the development of anti-drug antibodies (ADAs), which occur in approximately 50% of treated patients. Although neutralizing ADAs can attenuate biochemical responses, including slower reductions in uGAG levels, their direct impact on functional clinical outcomes, such as the 6MWT, remains variable. Nevertheless, they continue to pose a concern due to infusion-related hypersensitivity reactions.²⁰

The role of allogeneic hematopoietic stem cell transplantation (HSCT) in MPS II has historically been controversial. Unlike in MPS I (Hurler syndrome), early HSCT attempts in MPS II were associated with high morbidity and limited preservation of neurocognitive function.³¹ However, modern advancements in preconditioning regimens—including targeted busulfan and fludarabine—and improvements in donor matching have significantly reduced procedural mortality.³² Current evidence suggests that if HSCT is performed very early in the disease course, before the onset of symptoms or before 2 years of age, donor-derived engrafted microglia may provide a continuous source of I2S to the brain parenchyma, potentially stabilizing cognitive decline. Thus, very early HSCT is increasingly recognized as a viable option for carefully selected patients with neuronopathic disease.³³

CURRENT CHALLENGES, EMERGING FRONTIERS, AND FUTURE DIRECTIONS

Driven by the urgent need to address neuronopathic manifestations, recent therapeutic advances focus on pre-symptomatic detection and drug delivery strategies capable of bypassing the blood–brain barrier (BBB). A major historical hurdle in MPS II has been the diagnostic odyssey during which irreversible CNS and somatic damage occur before treatment is initiated. The inclusion of MPS II in NBS panels, such as the Recommended Uniform Screening Panel in the United States,

represents a monumental shift.⁸ However, NBS introduces a complex prognostic challenge: accurately predicting the clinical phenotype from the identified genotype in a pre-symptomatic neonate. While large structural deletions or complex rearrangements reliably predict the severe phenotype, private missense variants or variants of unknown significance complicate clinical decision-making. Accurate phenotypic prediction is imperative, as it dictates the risk-benefit justification for aggressive CNS-targeted early interventions, such as HSCT or experimental gene therapies.²⁵

Direct enzyme administration into the CSF through intrathecal or intracerebroventricular (ICV) delivery has emerged as a promising strategy for circumventing BBB limitations. Clinical studies evaluating ICV idursulfase beta, delivered via surgically implanted reservoirs, have demonstrated substantial reductions in CSF HS concentrations, accompanied by stabilization of neurodevelopmental decline, ultimately leading to regulatory approval in selected regions, including Japan.³⁴ A complementary non-invasive strategy relies on receptor-mediated transcytosis, often described as a “molecular Trojan horse” approach. In this method, the therapeutic IDS enzyme is fused to monoclonal antibodies that target BBB transcytosis receptors, particularly the human transferrin receptor. Following IV administration, receptor binding initiates transcytosis across the cerebrovascular endothelium, facilitating enzyme delivery into the brain parenchyma.³⁵ Pabinafusp alfa, currently approved in Japan, represents the first systemic ERT to demonstrate dual efficacy by reducing both somatic disease burden and CSF HS levels while stabilizing neurocognitive function. Similar investigational compounds, including tvidenofusp alfa, continue to advance through late-stage global clinical development.⁸

Beyond enzyme replacement strategies, next-generation therapeutic modalities increasingly focus on achieving sustained endogenous production of IDS through gene-based approaches. *In vivo* gene therapy using adeno-associated viral (AAV) vectors, particularly AAV9-based platforms such as RGX-121, has demonstrated encouraging early clinical results following intracisternal CNS delivery, including marked reductions in CSF biomarkers and sustained neurodevelopmental acquisition.³⁴ Alternatively, *ex vivo* lentiviral *hematopoietic stem cell* gene therapy involves harvesting autologous CD34+ stem cells, genetically modifying them to overexpress the *IDS* gene, and subsequently reinfusing them into the patient. Following engraftment, these cells may differentiate into brain microglia and provide continuous CNS enzyme production without the graft-versus-host disease risks associated with allogeneic HSCT. Genome-editing strategies also represent an emerging frontier. Early clinical investigations utilizing zinc finger nucleases, such as SB-913, have explored targeted insertion of the *IDS* transgene into the highly active albumin locus of hepatocytes

to facilitate durable systemic enzyme production.⁸ Although initial studies have demonstrated favorable safety profiles, achieving therapeutically meaningful and sustained enzyme expression remains an important challenge requiring further optimization.

CONCLUSION

MPS II is a relentlessly progressive, multisystem disorder. The introduction of IV ERT marked a historic milestone, fundamentally altering the natural history of somatic manifestations. While standard IV ERT has transformed systemic management, addressing neurological progression remains the cornerstone of modern research. Today, the management of Hunter syndrome is at a transformative crossroads. The synergistic integration of NBS programs with breakthrough technologies—such as BBB-crossing molecular Trojan horses, ICV enzyme administration, and advanced gene therapies—holds unprecedented promise. The ultimate goal of MPS II management is shifting from mere somatic palliation toward comprehensive disease correction, aiming to preserve neurocognitive capacity and restore normal quality of life for all affected individuals.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

REFERENCES

1. Bradley LA, Haddow HRM, Palomaki GE. Treatment of mucopolysaccharidosis type II (Hunter syndrome): results from a systematic evidence review. *Genet Med*. 2017;19(11):1187-1201. doi: 10.1038/gim.2017.30
2. D'Avanzo F, Rigon L, Zanetti A, Tomanin R. Mucopolysaccharidosis type II: one hundred years of research, diagnosis, and treatment. *Int J Mol Sci*. 2020;21(4):1258. doi: 10.3390/ijms21041258
3. Ago Y, Rintz E, Musini KS, Ma Z, Tomatsu S. Molecular mechanisms in pathophysiology of mucopolysaccharidosis and prospects for innovative therapy. *Int J Mol Sci*. 2024;25(2):1113. doi: 10.3390/ijms25021113
4. Derrick-Roberts A, Kaidonis X, Jackson MR, et al. Comparative analysis of brain pathology in heparan sulphate storing mucopolysaccharidoses. *Mol Genet Metab*. 2020;131(1-2):197-205. doi: 10.1016/j.ymgme.2020.07.006
5. Ausseil J, Desmaris N, Bigou S, et al. Early neurodegeneration progresses independently of microglial activation by heparan sulfate in the brain of mucopolysaccharidosis IIIB mice. *PLoS One*. 2008;3(5):e2296. doi: 10.1371/journal.pone.0002296
6. Mohamed S, He QQ, Singh AA, Ferro V. Mucopolysaccharidosis type II (Hunter syndrome): clinical and biochemical aspects of the disease and approaches to its diagnosis and treatment. *Adv Carbohydr Chem Biochem*. 2020;77:71-117. doi: 10.1016/bs.accb.2019.09.001
7. Mao SJ, Chen QQ, Dai YL, Dong GP, Zou CC. The diagnosis and management of mucopolysaccharidosis type II. *Ital J Pediatr*. 2024;50(1):207. doi: 10.1186/s13052-024-01769-9
8. Ream MA, Lam WKK, Grosse SD, et al. Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States. *Genet Med*. 2023;25(2):100330. doi: 10.1016/j.gim.2022.10.012

9. Burton BK, Amartino H, Giugliani R, et al. Female patients with mucopolysaccharidosis II (MPS II): insights from the hunter outcome survey. *JIMD Rep.* 2026;67(1):e70046. doi: 10.1002/jmd2.70046
10. Okuyama T, Tanaka A, Suzuki Y, et al. Japan Elaprase® Treatment (JET) study: idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (mucopolysaccharidosis II, MPS II). *Mol Genet Metab.* 2010;99(1):18-25. doi: 10.1016/j.ymgme.2009.08.006
11. Lin HY, Lin SP, Chuang CK, et al. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004. *Am J Med Genet A.* 2009;149A(5):960-964. doi: 10.1002/ajmg.a.32781
12. Khan SA, Peracha H, Ballhausen D, et al. Epidemiology of mucopolysaccharidoses. *Mol Genet Metab.* 2017;121(3):227-240. doi: 10.1016/j.ymgme.2017.05.016
13. Tulebayeva A, Mukhambetova G, Sharipova M, Tylki-Szymanska A. The birth prevalence of mucopolysaccharidoses types I, II, III, IVA, VI, and VII in the Republic of Kazakhstan between 1984 and 2023. *Diagnostics (Basel).* 2025;15(6):679. doi: 10.3390/diagnostics15060679
14. Hao N, Yao F, Li D, et al. Long-read sequencing expands the genotypic spectrum of patients with mucopolysaccharidosis type II. *J Inherit Metab Dis.* 2025;48(4):e70055. doi: 10.1002/jimd.70055
15. Scarpa M, Almássy Z, Beck M, et al. Hunter Syndrome Europea Expert Council. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet J Rare Dis.* 2011;6:72. doi: 10.1186/1750-1172-6-72
16. Malm G, Lund AM, Månsson JE, Heiberg A. Mucopolysaccharidoses in the Scandinavian countries: incidence and prevalence. *Acta Paediatr.* 2008;97:1577-1581. doi: 10.1111/j.1651-2227.2008.00965.x. Erratum in: *Acta Paediatr.* 2008;97(12):1773.
17. Ayodele O, Fertek D, Evuarherhe O, Siffel C, Audi J, Yee KS, Burton BK. A systematic literature review on the global status of newborn screening for mucopolysaccharidosis II. *Int J Neonatal Screen.* 2024;10(4):71. doi: 10.3390/ijns10040071
18. Krabbi K, Joost K, Zordania R, et al. The live-birth prevalence of mucopolysaccharidoses in Estonia. *Genet Test Mol Biomarkers.* 2012;16(8):846-849. doi: 10.1089/gtmb.2011.0307
19. Seo JH, Okuyama T, Shapiro E, Fukuhara Y, Kosuga M. Natural history of cognitive development in neuronopathic mucopolysaccharidosis type II (Hunter syndrome): Contribution of genotype to cognitive developmental course. *Mol Genet Metab Rep.* 2020;24:100630. doi: 10.1016/j.ymgmr.2020.100630
20. Muenzer J, Botha J, Amartino H, et al. Clinical characteristics and real-world outcomes in patients with mucopolysaccharidosis II over 18 years: final report of the hunter outcome survey. *Mol Genet Metab.* 2025;146(4):109284. doi: 10.1016/j.ymgme.2025.109284
21. Bhalla A, Ravi R, Fang M, et al. Characterization of fluid biomarkers reveals lysosome dysfunction and neurodegeneration in neuronopathic MPS II patients. *Int J Mol Sci.* 2020;21(1):5188. doi: 10.3390/ijms21155188
22. Leal GN, de Paula AC, Leone C, Kim CA. Echocardiographic study of paediatric patients with mucopolysaccharidosis. *Cardiol Young.* 2010;20(3):254-261. doi: 10.1017/S104795110999062X
23. Yazıcı H, Kara E, Bulut FD, et al. Genotype–phenotype correlations and shifting diagnosis age in Turkish mucopolysaccharidosis type II patients: a multicenter retrospective study. *Diagnostics (Basel).* 2025;15(21):2773. doi: 10.3390/diagnostics15212773
24. Tomatsu S, Pitz S, Hampel U. Ophthalmological findings in mucopolysaccharidoses. *J Clin Med.* 2019;8(9):1467. doi: 10.3390/jcm8091467
25. Scarpa M, Lampe C. Mucopolysaccharidosis type II. 2007 Nov 6 [updated 2026 Apr 28]. In: Adam MP, Bick S, Mirzaa GM, Wallace SE, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026.
26. Vollebregt AAM, Hoogveen-Westerveld M, Kroos MA, et al. Genotype-phenotype relationship in mucopolysaccharidosis II: predictive power of IDS variants for the neuronopathic phenotype. *Dev Med Child Neurol.* 2017;59(10):1063-1070. doi: 10.1111/dmcn.13467
27. Li P. Molecular analyses in families with hunter syndrome indicate unequal male and female mutation rates in the iduronate-2-sulfatase gene. *J Mol Genet Med.* 2014;8:1000135. doi: 10.4172/1747-0862.1000135
28. Schwartz IVD, Pinto LLC, Breda G, et al. Clinical and biochemical studies in mucopolysaccharidosis type II carriers. *J Inherit Metab Dis.* 2009;32(6):732-738. doi: 10.1007/s10545-009-1275-9
29. Sahin O, Thompson HP, Goodman GW, Li J, Urayama A. Mucopolysaccharidoses and the blood-brain barrier. *Fluids Barriers CNS.* 2022;19(1):76. doi: 10.1186/s12987-022-00373-5
30. Huang L, Wu J, Tang B, et al. Efficacy of different treatment strategies in patients with mucopolysaccharidosis: a systematic review and network meta-analysis of randomized controlled trials. *Orphanet J Rare Dis.* 2025;20(1):211. doi: 10.1186/s13023-025-03735-y
31. Xu Y, Fang X, Luo C, et al. Allogeneic hematopoietic stem cell transplantation modulates neurodevelopmental trajectories in mucopolysaccharidosis: a longitudinal study of subtype-specific outcomes and age-dependent efficacy. *Orphanet J Rare Dis.* 2025;20(1):591. doi: 10.1186/s13023-025-04025-3
32. Barth AL, de Magalhães TSPC, Reis ABR, et al. Early hematopoietic stem cell transplantation in a patient with severe mucopolysaccharidosis II: a 7 years follow-up. *Mol Genet Metab Rep.* 2017;12:62-68. doi: 10.1016/j.ymgmr.2017.05.010
33. Sreekantam S, Smith L, Stewart C, et al. Efficacy of early haematopoietic stem cell transplantation versus enzyme replacement therapy on neurological progression in severe hunter syndrome: case report of siblings and literature review. *Mol Genet Metab Rep.* 2022;32:100881. doi: 10.1016/j.ymgmr.2022.100881
34. Zanetti A, Tomanin R. Targeting neurological aspects of mucopolysaccharidosis type II: enzyme replacement therapy and beyond. *biodrugs.* 2024;38(5):639-655. doi: 10.1007/s40259-024-00675-0
35. Sonoda H, Takahashi K, Minami K, et al. Treatment of neuronopathic mucopolysaccharidoses with blood–brain barrier-crossing enzymes: clinical application of receptor-mediated transcytosis. *Pharmaceutics.* 2022;14(6):1240. doi: 10.3390/pharmaceutics14061240