Review Article

J Mucopolysacch Rare Dis 2017;3(1):1-8
https://doi.org/10.19125/jmrd.2017.3.1.1
pISSN 2465-8936 · eISSN 2465-9452

JMRD
Journal of Mucopolysaccharidosis and Rare Diseases

Mucopolysaccharidosis Type III: Overview and Future Therapeutic Approaches

Min Jung Kwak

Department of Pediatrics, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Korea

Mucopolysaccharidosis (MPS) type III, or Sanfilippo syndrome is a rare autosomal recessive lysosomal storage disorder. It is caused by a deficiency of one of four enzymes involved in the degradation of the glycosaminoglycan (GAG) heparan sulfate. The resultant cellular accumulation of heparan sulfate causes various clinical manifestations. MPS III is divided into four subtypes depending on the deficient enzyme: MPS IIIA, MPS IIIB, MPS IIIC and MPS IIID. All the subtypes show similar clinical features and are characterized by progressive degeneration of the central nervous system (CNS). Main purpose of the treatment for MPS III is to prevent neurologic deterioration. However, conventional enzyme replacement therapy has a limitation due to inability to cross the blood-brain barrier. Several experimental treatment options for MPS III are being developed.

Keywords: Mucopolysaccharidosis type III, Sanfilippo syndrome, Treatment

Introduction

Mucopolysaccharidosis (MPS) type III, or Sanfilippo syndrome is a rare autosomal recessive lysosomal storage disorder[1,2]. It is caused by a deficiency of one of four enzymes involved in the degradation of the glycosaminoglycan (GAG) heparan sulfate[3-6]. The resultant cellular accumulation of heparan sulfate causes various clinical manifestations. MPS III is divided into four subtypes depending on the deficient enzyme: MPS IIIA (N-sulfoglucosamine sulfohydrolase, also known as sulfamidase or heparan sulfate sulfatase); MPS IIIB (N-alpha-acetylglucosaminidase); MPS IIIC (heparan acetyl-CoA:alpha-glucosaminide N-acetyltransferase); MPS IIID (N-acetylglucosamine-6-sulfatase)[3-6]. All the subtypes show similar clinical features and are characterized by progressive degeneration of the central nervous system (CNS)[7]. Typical features of MPS may be present, although milder than in other types of MPS[8]. This leads delayed diagnosis of MPS III. Patients with MPS III usually present between the age of 1 and 6 years with developmental delay and/or behavioral problems such as hyperactivity and aggression[9,10]. Neurologic deterioration progresses to a vegetative state and death can occur anywhere between the early teens and the sixth decade[10-15]. Incidences of MPS III range from 0.39 per 100,000 live births in Taiwan to 1.89 per 100,000 live births in The Netherlands[9,16-19]. MPS III is the most common type of MPS around the world[20]. By contrast, MPS III accounts for 18% of Korean patients with MPS that is the second most common after MPS II (64%)[21]. Currently, there is no available therapy for MPS III. Experimental trials with animal models for MPS III are in progress[22-27]. In this review causes, clinical features, diagnosis and current therapeutic approaches to MPS III will be presented.

Classification

MPS III is characterized by the accumulation of heparan sulfate in lysosomes and increased excretion of it in urine. MPS III occurs in 4 forms depending on the deficient enzyme. Heparan sulfate is a negatively charged polysaccharide covalently bound

Received May 23, 2017; **Revised** May 25, 2017; **Accepted** June 2, 2017
Correspondence to: Min Jung Kwak
Department of Pediatrics, Pusan National University Hospital, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea
Tel: +82-51-240-7298, Fax: +82-51-248-6205, E-mail: glorymj0123@gmail.com

to various proteins at the cell surface and in the extracellular matrix[28]. Degradation of heparan sulfate commences with endolytic cleavage by heparanase, resulting in heparan oligosaccharide fragments. Subsequent degradation occurs by sequential exolytic processes in the lysosomes which involve three exoglycosidases, at least three sulfatases and an acetyltransferase. Four of these enzymes are specific for heparan sulfate and a deficiency of each leads to MPS IIIA, MPS IIIB, MPS IIIC and MPS IIID. MPS IIIA (MIM #252900) results from mutations in the gene encoding N-sulfoglucosamine sulfohydrolase (SGSH; EC 3.10.1.1), also known as sulfamidase or heparan sulfate sulfatase[3]. MPS IIIB (MIM #252920) results from mutations in the gene encoding N-alpha-acetylglucosaminidase (NAGLU; EC 3.2.1.50)[4]. MPS IIIC (MIM #252930) results from mutations in the gene encoding heparan acetyl-CoA:alpha-glucosaminide N-acetyltransferase (HGSNAT; EC 2.3.1.78)[5]. MPS IIID (MIM #252940) results from mutations in the gene encoding N-acetylglucosamine-6-sulfatase (GNS; EC 3.1.6.14)[6]. Classification of MPS III subtypes are summarized in Table 1.

Genetic Aspects

Homozygous or compound heterozygous mutation in the causative gene causes one of the subtypes of MPS III. Most mutations are private but some of them are frequently found in distinct geographical regions. The kind of mutation affects the residual enzyme activity consequently clinical severity. The correlation between genotype and phenotype is uncertain.

1. MPS IIIA

The gene encoding SGSH is localized to chromosome 17q25.3 and contains 8 exons[3,29]. The SGSH cDNA encodes a protein of 502 amino acids with five potential N-glycosylation sites[3]. So far, 143 different mutations have been reported. These include 98 misssense mutations, 11 nonsense mutations, 3 splice site mutations, 17 small deletions and 9 small insertions (Table 2)[30]. R245H mutation was common in Germany (35% of the mutant alleles)[31] and The Netherlands (57% of the mutant alleles)[32]. S66W mutation is frequent in Italy (29% of the mutant alleles)[33]. R74C and 1079delC mutations were frequent in Poland (56% of the mutant alleles) and Spain (45% of the mutant alleles) respectively[31,34]. R245H, S66W, Q380R and 1080delC mutations are known to be associated with the severe phenotype[11]. S298P, T421R, P180L, L12Q and R206P mutations are considered to show an attenuated phenotype with a longer preservation of psychomotor functions and a longer survival[11,35].

Table 1. Classification of the subtypes of MPS III

Subtype	Deficient enzyme	Phenotype MIM number	Gene/Locus	Cytogenetic location
MPS IIIA	N-sulfoglucosamine sulfohydrolase	252,900	SGSH	17q25.3
MPS IIIB	N-alpha-acetylglucosaminidase	252,920	NAGLU	17q21.1
MPS IIIC	Heparan acetyl-CoA: alpha-glucosaminide N-acetyltrasnferase	252,930	HGSNAT	8p11.1
MPS IIID	N-acetylglucosamine-6-sulfatase	252,940	GNS	12q14.3

MPS, Mupopolysaccharidosis; SGSH, N-sulfoglucosamine sulfohydrolase, also known as sulfamidase or heparan sulfate sulfatase; NAGLU, N-alpha-acetylglucosaminidase; HGSNAT, Heparan acetyl-CoA:alpha-glucosaminide N-acetyltrasnferase; GNS, N-acetylglucosamine-6-sulfatase.

Table 2. Mutation types and numbers found in the alleles of four genes for MPS III

Subtype	Gens	Total	Missense	Nonsense	Splicing	Small deletion	Small insertion	Small indels	Gross deletions	Gross insertions	Complex rearrangement
MPS IIIA	*SGSH*	143	98	11	3	17	9	1	3	1	0
MPS IIIB	*NAGLU*	163	97	14	6	25	13	1	4	3	0
MPS IIIC	*HGSNAT*	65	27	9	14	5	5	1	2	1	1
MPS IIID	*GNS*	25	3	4	4	5	4	1	2	0	2

Data from The Human Gene Mutation Database (http://www.hgmd.org). Cardiff University, 2017. Accessed May 13th, 2017.
MPS, mucopolysaccharidosis.

2. MPS IIIB

The gene encoding NAGLU is localized to chromosome 17q21.1[4]. The cDNA encodes a protein of 743 amino acids with six potential N-glycosylation sites[36]. Currently 163 different mutations have been reported. These include 97 missense mutations, 14 nonsense mutations, 6 splice site mutations, 25 small deletions and 13 small insertions (Table 2)[30]. Recurrent mutations are very rare. F48L, G69S, S612G and R643C mutations are associated with mild phenotype[37]. In Korea, R482W mutation has been reported in two patients with MPS IIIB[38,39].

3. MPS IIIC

The gene encoding HGSNAT is localized to chromosome 8p11.1 and contains 18 exons[5]. HGSNAT cDNA encodes a protein of 635 amino acids, which contains 11 transmembrane domains and 5 potential N-glycosylation sites[40,41]. To date, 65 different mutations have been reported. These include 27 missense mutations, 9 nonsense mutations, 14 splice site mutations, 5 small deletions and 5 small insertions (Table 2)[30]. R344C and S518F mutations (22% and 29% of the mutant alleles respectively) were common in The Netherlands[10]. G262R and S539C mutations are considered to show an attenuated phenotype[10]. 372-2A>G and 234+1G>A mutations were common in a study including 7 Spanish patients, 1 Argentinean and 3 Moroccan patients[42]. Compound heterozygous mutation for previously reported 234+1G>A and R384X was found in a Korean patients with MPS IIIC[43].

4. MPS IIID

The gene encoding GNS is localized to chromosome 12q14 and contains 14 exons[6]. The cDNA encodes a protein of 552 amino acids with 13 potential N-glycosylation sites[6]. So far, 25 different mutations have been reported. These include 3 missense mutations, 4 nonsense mutations, 5 small deletions, 4 small insertions and 2 rearrangements[30]. There are fewer missense and nonsense mutations compared with the other MPS III subtypes. Also there are no common mutations in MPS IIID patients.

Clinical Features

Clinical features of MPS III include severe neurological defect with relatively mild somatic manifestations compared with other forms of MPS[7,8]. Somatic symptoms are coarse facial appearance with broad eyebrows, dark eyelashes, dry and rough hair, hepatosplenogemaly, enlarged tongue, hearing loss and dysostosis multiplex[8,10,15,44]. Subtypes of MPS III are clinically similar and indistinguishable. However, there are reports that the clinical course in MPS IIIA is more severe with earlier onset, more rapid progression of symptoms and earlier death[10,15,45].

Patients with MPS III usually present between the age of 1 and 6 years[9,10]. Prenatal and early development is typically normal. The most common initial symptom is speech/language delay (48%), followed by dysmorphology (22%), and hearing loss (20%)[44]. Early behavioral problems include perseverative chewing and difficulty with toilet training[44]. Other behavioral problems are hyperactivity, anxiety and aggression which are frequently very hard to manage[10,46,47]. Most patients also develop sleep disorders[47-49]. Sleep problems include settling difficulties, early waking and frequent nocturnal waking. Behavioral problems regress with age and finally disappear due to the progressive mental retardation and loss of motor function including swallowing and walking[11-13]. Patients with MPS III eventually become a vegetative state and die anywhere between the second and the sixth decade of life[10].

Diagnosis

1. Urinary GAG analysis

The detection of heparan sulfate in the urine is the first step in the diagnosis for suspected MPS III patients. Both a quantitative test of total GAG and a fractionation method such as electrophoresis should be used. When urinary excretion of total GAG is elevated, electrophoretic separation of GAGs can establish the different types of GAGs[50]. Increased excretion of only heparan sulfate indicates MPS III. Urine testing may be falsely negative in MPS III due to lower urinary GAG levels and smaller heparan sulfate fragments than in the other types of MPS[50]. Therefore, enzyme assay should be performed in suspected MPS III patients with normal urinary GAG excretion. A liquid chromatography/tandem mass spectrometry method (LC-MS/MS) is recently developed. LC-MS/MS can quantify the types of GAGs and is more sensitive, specific and less time-consuming than electrophoresis[51,52]. The quantification of urinary GAGs has a limitation that it cannot distinguish the MPS III subtypes. Although, that is a useful initial screening test.

2. Enzyme assay

Enzyme assay in peripheral blood leukocytes or cultured fibroblasts provides definitive diagnosis of MPS III and classification of the subtype[53-56]. Patients with MPS III show markedly decreased enzyme activity. Enzyme assay has limited use for carrier detection because there is considerable overlap of the levels of enzyme activity between carriers and unaffected controls.

3. DNA sequencing

Direct DNA sequencing of the causative gene can confirm the subtypes of MPS III. Also, it is useful to detect carriers among siblings or other relatives when the mutation is known. However, it cannot detect large deletions which frequently occur in MPS IIID.

4. Other studies

Additional studies including neurologic examination, hearing test, and radiographic examination etc. are needed to evaluate the affected organs.

5. Prenatal diagnosis

Prenatal diagnosis can be performed using material obtained by chorionic villous sampling and amniocenteces[57]. GAGs analysis, enzyme assay and DNA sequencing can be used for this purpose.

Management

Currently, there is no effective therapy for the CNS involvement of MPS III. Therefore, primary efforts are focused to manage behavior and sleep problems. Treatment of the CNS deterioration in MPS III is challenging and several potential therapies are being developed.

1. Management of behavior and sleep problems

The behavior problems respond poorly to a behavioral approach to treatment. The response to drug treatment is very unpredictable. Antipsychotic drugs such as thioridazine hydrochloride and haloperidol can be useful[20].

Management of sleep problems is also very difficult. Many parents use physical restraint at night to prevent children from getting out of bed[20]. Among the medications, melatonin is effective in approximately 75% of patients. Benzodiazepines, chloral hydrate, antihistamines and antipsychotic agents are reported as less effective[49].

2. Enzyme replacement therapy (ERT)

ERT is currently available for patients with MPS I, MPS II, MPS IVA, and MPS VI[58]. The limitation of ERT for MPS III is that peripherally administered enzyme cannot cross the blood-brain barrier. High dose, chemically modified sulfamidase without mannose-6-phosphate glycans was administered intravenously in a murine model of MPS IIIA. Chemical modification made lower doses of recombinant human SGSH (rhSGSH) to increase systemic delivery. However, it was not effective in the brain[59]. Injection of rhSGSH directly into the brain or into cerebrospinal fluid (CSF) of MPS IIIA mice has been effective in reducing brain pathology[60,61]. A clinical trial of CSF infusion of rhSGSH is being undertaken. Recently low dose, continuous delivery of rhSGSH using subcutaneously placed osmotic pumps connected to a unilateral intraventricular cannula in the mouse model of MPS III is reported that heparan sulfate in both hemispheres of the MPS IIIA brain and cervical spinal cord is nearly normalized[23].

3. Hematopoietic cell transplantation (HCT)

HCT by bone marrow transplantation was not successful in MPS III patients, in contrast to some other neuropathic MPS[62]. Umbilical cord blood-derived stem cell transplantation did not prevent neurologic deterioration of MPS III patients, even when performed before clinical onset of CNS disease[63].

4. Gene therapy

Gene therapy introduce the coding sequence of the enzyme into cells of the patients using a viral vector. The altered cells will have enzymatic activity and secrete it into circulation to be taken up by other cells. Administration of serotype 9 adeno-associated viral vectors (AAV9s) encoding SGSH into CSF of MPS IIIA mice resulted in increased enzymatic activity throughout the brain and in serum, decreased CNS pathology, normalization of behavioral deficits and prolonged survival[64]. Sulfatase-modifying factor (SUMF1) activates the catalytic site of SGSH. Co-delivery of SGSH and SUMF1 via intracerebral administration in children with MPS IIIA is being undertaken[65].

5. Substrate reduction therapy

Substrate reduction therapy aimes at inhibiting the synthesis of GAGs to a point where residual enzymatic activity is sufficient to prevent accumulation of GAGs. Substrate reduction therapy uses small molecules with the ability to across the blood-brain barrier. Therefore they are expected to have potential for the treatment of MPS III. Several molecules have been suggested.

Rhodamine B is a non-specific inhibitor of GAG synthesis. Rhodamine B reduced GAG contents in brain and urine, decreased liver size, improved CNS functions in a mouse model of MPS IIIA[66,67]. There were no significant adverse effects in MPS IIIA mice with low dose treatment of rhodamine B[68].

Genistein is an isoflavone that inhibits kinase activity of epidermal growth factor receptor, which is required for full expression of genes coding for enzymes involved in GAG production. Genistein inhibited synthesis of GAGs considerably in cultured skin fibroblasts from patients with MPS IIIA and IIIB[69]. In a mouse model of MPS IIIB, genistein reduced heparan sulfate in liver and brain, improved neuropathology and corrected behavior defects[70]. Recently, a genistein-rich soy isoflavone extract in patients with MPS IIIA and IIIB, resulted in a decrease in the urinary GAG levels, normalization of hair morphology and improvement of neurologic symptoms including inhibition of developmental regression, improved sleep and decreased hyperactivity[71].

Oral treatment with N-butyldeoxynojirimycin (OGT 918, miglustat) has been developed for type I Gaucher disease (non-neuropathic), resulting in decreased substrate formation and improvement of clinical features[72]. Miglustat reversibly inhibits glucosylceramide synthase, an essential enzyme for the synthesis of most glycosphingolipids. Miglustat is able to cross the blood-brain barrier, and is thus a potential therapy for neurological diseases. A recent clinical study in patients with Niemann-Pick disease type C was reported that miglustat had improved or stabilized several neurologic manifestations of Neimann-Pick disease type C[73]. However, one year of miglustat treatment was not associated with any improvement or stabilization of behavior problems in patients with MPS III[74].

6. Molecular chaperone therapy

Most of missense mutations result in midfolding of enzyme and ultimately rapid degradation of enzyme in lysosomes. Molecular chaperones are small molecules that can correct the misfolding of enzyme. They are typically reversible competitive inhibitors which can bind active-site of enzyme, induce normal folding of enzyme, resulting in restoration of enzyme activity[75]. Glucosamine is a competitive inhibitor of the HGSNAT. It was reported that glucosamine increased HGSNAT activity in cultured fibroblasts from MPS IIIC patient carrying with several missense mutations[76]. Modified U1 spliceosomal small nuclear RNAs improved recognition of the donor splice sites of selected splice site mutations and enhanced the correct splicing process in cultured fibroblasts from patients with MPS IIIC[27]. Clinical trials on this approach have not yet been published.

Conclusion

MPS III is characterized by progressive degeneration of the CNS. Early death in teens occurs in severe phenotype. New treatment modalities are needed due to a limitation of a conventional enzyme replacement therapy in patients with MPS III. Study results of substrate reduction therapy and molecular chaperone therapy in MPS III animal models are promising. It suggests that they might be potential future therapies. Clinical trials with them in MPS III patients are necessary.

References

1. Muenzer J. Mucopolysaccharidoses. Adv Pediatr 1986;33:269-302.
2. Wraith JE. The mucopolysaccharidoses: a clinical review and guide to management. Arch Dis Child 1995;72:263-7.
3. Scott HS, Blanch L, Guo XH, Freeman C, Orsborn A, Baker E, et al. Cloning of the sulphamidase gene and identification of mutations in Sanfilippo A syndrome. Nat Genet 1995;11:465-7.
4. Zhao HG, Li HH, Bach G, Schmidtchen A, Neufeld EF. The molecular basis of Sanfilippo syndrome type B. Proc Natl Acad Sci U S A 1996;93:6101-5.
5. Fan X, Zhang H, Zhang S, Bagshaw RD, Tropak MB, Callahan JW, et al. Identification of the gene encoding the enzyme deficient in mucopolysaccharidosis IIIC (Sanfilippo disease type C). Am J Hum Genet 2006;79:738-44.
6. Robertson DA, Callen DF, Baker EG, Morris CP, Hopwood JJ. Chromosomal localization of the gene for human glucosamine-6-sulphatase to 12q14. Hum Genet 1988;79:175-8.
7. Shapiro EG, Nestrasil I, Delaney KA, Rudser K, Kovac V, Nair N, et al. A prospective natural history study of mucopolysaccharidosis type IIIA. J Pediatr 2016;170:278-87.e1-4.
8. White KK, Karol LA, White DR, Hale S. Musculoskeletal manifestations of Sanfilippo syndrome (mucopolysacchari-

dosis type III). J Pediatr Orthop 2011;31:594-8.
9. Heron B, Mikaeloff Y, Froissart R, Caridade G, Maire I, Caillaud C, et al. Incidence and natural history of mucopolysaccharidosis type III in France and comparison with United Kingdom and Greece. Am J Med Genet A 2011;155a:58-68.
10. Ruijter GJ, Valstar MJ, van de Kamp JM, van der Helm RM, Durand S, van Diggelen OP, et al. Clinical and genetic spectrum of Sanfilippo type C (MPS IIIC) disease in The Netherlands. Mol Genet Metab 2008;93:104-11.
11. Valstar MJ, Neijs S, Bruggenwirth HT, Olmer R, Ruijter GJ, Wevers RA, et al. Mucopolysaccharidosis type IIIA: clinical spectrum and genotype-phenotype correlations. Ann Neurol 2010;68:876-87.
12. Valstar MJ, Bruggenwirth HT, Olmer R, Wevers RA, Verheijen FW, Poorthuis BJ, et al. Mucopolysaccharidosis type IIIB may predominantly present with an attenuated clinical phenotype. J Inherit Metab Dis 2010;33:759-67.
13. Valstar MJ, Bertoli-Avella AM, Wessels MW, Ruijter GJ, de Graaf B, Olmer R, et al. Mucopolysaccharidosis type IIID: 12 new patients and 15 novel mutations. Hum Mutat 2010;31:E1348-60.
14. Nidiffer FD, Kelly TE. Developmental and degenerative patterns associated with cognitive, behavioural and motor difficulties in the Sanfilippo syndrome: an epidemiological study. J Ment Defic Res 1983;27 (Pt 3):185-203.
15. van de Kamp JJ, Niermeijer MF, von Figura K, Giesberts MA. Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (types A, B, and C). Clin Genet 1981;20:152-60.
16. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-54.
17. Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 1999;105:151-6.
18. Baehner F, Schmiedeskamp C, Krummenauer F, Miebach E, Bajbouj M, Whybra C, et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis 2005;28:1011-7.
19. Lin HY, Lin SP, Chuang CK, Niu DM, Chen MR, Tsai FJ, et al. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004. Am J Med Genet A 2009;149a:960-4.
20. Cleary MA, Wraith JE. Management of mucopolysaccharidosis type III. Arch Dis Child 1993;69:403-6.
21. Sohn WY, Lee JH, Paik KH, Kwon EK, Kim AH, Jin DK. Clinical and laboratory features of Korean mucopolysaccharidoses (MPSs). Korean J Pediatr 2005;48:1132-8.
22. Winner LK, Beard H, Hassiotis S, Lau AA, Luck AJ, Hopwood JJ, et al. A preclinical study evaluating AAVrh10-based gene therapy for Sanfilippo syndrome. Hum Gene Ther 2016;27:363-75.
23. King B, Hassiotis S, Rozaklis T, Beard H, Trim PJ, Snel MF, et al. Low-dose, continuous enzyme replacement therapy ameliorates brain pathology in the neurodegenerative lysosomal disorder mucopolysaccharidosis type IIIA. J Neurochem 2016;137:409-22.
24. Gilkes JA, Bloom MD, Heldermon CD. Preferred transduction with AAV8 and AAV9 via thalamic administration in the MPS IIIB model: A comparison of four rAAV serotypes. Mol Genet Metab Rep 2016;6:48-54.
25. Coutinho MF, Santos JI, Alves S. Less is more: Substrate reduction therapy for lysosomal storage disorders. Int J Mol Sci 2016;17.
26. Canals I, Beneto N, Cozar M, Vilageliu L, Grinberg D. EXTL2 and EXTL3 inhibition with siRNAs as a promising substrate reduction therapy for Sanfilippo C syndrome. Sci Rep 2015;5:13654.
27. Matos L, Canals I, Dridi L, Choi Y, Prata MJ, Jordan P, et al. Therapeutic strategies based on modified U1 snRNAs and chaperones for Sanfilippo C splicing mutations. Orphanet J Rare Dis 2014;9:180.
28. Kjellen L, Lindahl U. Proteoglycans: structures and interactions. Annu Rev Biochem 1991;60:443-75.
29. Karageorgos LE, Guo XH, Blanch L, Weber B, Anson DS, Scott HS, et al. Structure and sequence of the human sulphamidase gene. DNA Res 1996;3:269-71.
30. Cooper DN, Ball EV, Stenson PD, Phillips AD, Evans K, Heywood S, et al. The human gene mutation database [Internet]. Cardiff University, 2017 [cited 2017 May 13]. Available from: http://www.hgmd.org.
31. Bunge S, Ince H, Steglich C, Kleijer WJ, Beck M, Zaremba J, et al. Identification of 16 sulfamidase gene mutations including the common R74C in patients with mucopolysaccharidosis type IIIA (Sanfilippo A). Hum Mutat 1997;10:479-85.
32. Weber B, Guo XH, Wraith JE, Cooper A, Kleijer WJ, Bunge S, et al. Novel mutations in Sanfilippo A syndrome: implications for enzyme function. Hum Mol Genet 1997;6:1573-9.
33. Di Natale P, Balzano N, Esposito S, Villani GR. Identification of molecular defects in Italian Sanfilippo A patients including 13 novel mutations. Hum Mutat 1998;11:313-20.
34. Montfort M, Vilageliu L, Garcia-Giralt N, Guidi S, Coll MJ, Chabas A, et al. Mutation 1091delC is highly prevalent in Spanish Sanfilippo syndrome type A patients. Hum Mutat

1998;12:274-9.
35. Gabrielli O, Coppa GV, Bruni S, Villani GR, Pontarelli G, Di Natale P. An adult Sanfilippo type A patient with homozygous mutation R206P in the sulfamidase gene. Am J Med Genet A 2005;133a:85-9.
36. Weber B, Blanch L, Clements PR, Scott HS, Hopwood JJ. Cloning and expression of the gene involved in Sanfilippo B syndrome (mucopolysaccharidosis III B). Hum Mol Genet 1996;5:771-7.
37. Yogalingam G, Hopwood JJ. Molecular genetics of mucopolysaccharidosis type IIIA and IIIB: Diagnostic, clinical, and biological implications. Hum Mutat 2001;18:264-81.
38. Kim YE, Park HD, Jang MA, Ki CS, Lee SY, Kim JW, et al. A novel mutation (c.200T>C) in the NAGLU gene of a Korean patient with mucopolysaccharidosis IIIB. Ann Lab Med 2013;33:221-4.
39. Kim JH, Chi YH, Kim GH, Yoo HW, Lee JH. Long-term clinical course of a patient with mucopolysaccharidosis type IIIB. Korean J Pediatr 2016;59:S37-40.
40. Hrebicek M, Mrazova L, Seyrantepe V, Durand S, Roslin NM, Noskova L, et al. Mutations in TMEM76* cause mucopolysaccharidosis IIIC (Sanfilippo C syndrome). Am J Hum Genet 2006;79:807-19.
41. Fan X, Tkachyova I, Sinha A, Rigat B, Mahuran D. Characterization of the biosynthesis, processing and kinetic mechanism of action of the enzyme deficient in mucopolysaccharidosis IIIC. PLoS One 2011;6:e24951.
42. Canals I, Elalaoui SC, Pineda M, Delgadillo V, Szlago M, Jaouad IC, et al. Molecular analysis of Sanfilippo syndrome type C in Spain: seven novel HGSNAT mutations and characterization of the mutant alleles. Clin Genet 2011;80:367-74.
43. Huh HJ, Seo JY, Cho SY, Ki CS, Lee SY, Kim JW, et al. The first Korean case of mucopolysaccharidosis IIIC (Sanfilippo syndrome type C) confirmed by biochemical and molecular investigation. Ann Lab Med 2013;33:75-9.
44. Buhrman D, Thakkar K, Poe M, Escolar ML. Natural history of Sanfilippo syndrome type A. J Inherit Metab Dis 2014;37:431-7.
45. Meyer A, Kossow K, Gal A, Muhlhausen C, Ullrich K, Braulke T, et al. Scoring evaluation of the natural course of mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A). Pediatrics 2007;120:e1255-61.
46. Wraith JE, Danks DM, Rogers JG. Mild Sanfilippo syndrome: a further cause of hyperactivity and behavioural disturbance. Med J Aust 1987;147:450-1.
47. Bax MC, Colville GA. Behaviour in mucopolysaccharide disorders. Arch Dis Child 1995;73:77-81.
48. Colville GA, Watters JP, Yule W, Bax M. Sleep problems in children with Sanfilippo syndrome. Dev Med Child Neurol 1996;38:538-44.
49. Fraser J, Wraith JE, Delatycki MB. Sleep disturbance in mucopolysaccharidosis type III (Sanfilippo syndrome): a survey of managing clinicians. Clin Genet 2002;62:418-21.
50. Stone JE. Urine analysis in the diagnosis of mucopolysaccharide disorders. Ann Clin Biochem 1998;35 (Pt 2):207-25.
51. Chuang CK, Lin HY, Wang TJ, Tsai CC, Liu HL, Lin SP. A modified liquid chromatography/tandem mass spectrometry method for predominant disaccharide units of urinary glycosaminoglycans in patients with mucopolysaccharidoses. Orphanet J Rare Dis 2014;9:135.
52. Fuller M, Rozaklis T, Ramsay SL, Hopwood JJ, Meikle PJ. Disease-specific markers for the mucopolysaccharidoses. Pediatr Res 2004;56:733-8.
53. Karpova EA, Voznyi Ya V, Keulemans JL, Hoogeveen AT, Winchester B, Tsvetkova IV, et al. A fluorimetric enzyme assay for the diagnosis of Sanfilippo disease type A (MPS IIIA). J Inherit Metab Dis 1996;19:278-85.
54. Marsh J, Fensom AH. 4-Methylumbelliferyl alpha-N-acetylglucosaminidase activity for diagnosis of Sanfilippo B disease. Clin Genet 1985;27:258-62.
55. Voznyi Ya V, Karpova EA, Dudukina TV, Tsvetkova IV, Boer AM, Janse HC, et al. A fluorimetric enzyme assay for the diagnosis of Sanfilippo disease C (MPS III C). J Inherit Metab Dis 1993;16:465-72.
56. He W, Voznyi Ya V, Boer AM, Kleijer WJ, van Diggelen OP. A fluorimetric enzyme assay for the diagnosis of Sanfilippo disease type D (MPS IIID). J Inherit Metab Dis 1993;16:935-41.
57. Fensom AH, Benson PF. Recent advances in the prenatal diagnosis of the mucopolysaccharidoses. Prenat Diagn 1994;14:1-12.
58. Dietz HC. New therapeutic approaches to mendelian disorders. N Engl J Med 2010;363:852-63.
59. Rozaklis T, Beard H, Hassiotis S, Garcia AR, Tonini M, Luck A, et al. Impact of high-dose, chemically modified sulfamidase on pathology in a murine model of MPS IIIA. Exp Neurol 2011;230:123-30.
60. Hemsley KM, King B, Hopwood JJ. Injection of recombinant human sulfamidase into the CSF via the cerebellomedullary cistern in MPS IIIA mice. Mol Genet Metab 2007;90:313-28.
61. Savas PS, Hemsley KM, Hopwood JJ. Intracerebral injection

of sulfamidase delays neuropathology in murine MPS-IIIA. Mol Genet Metab 2004;82:273-85.
62. Sivakumur P, Wraith JE. Bone marrow transplantation in mucopolysaccharidosis type IIIA: a comparison of an early treated patient with his untreated sibling. J Inherit Metab Dis 1999;22:849-50.
63. Welling L, Marchal JP, van Hasselt P, van der Ploeg AT, Wijburg FA, Boelens JJ. Early umbilical cord blood-derived stem cell transplantation does not prevent neurological deterioration in mucopolysaccharidosis type III. JIMD Rep 2015;18:63-8.
64. Haurigot V, Marco S, Ribera A, Garcia M, Ruzo A, Villacampa P, et al. Whole body correction of mucopolysaccharidosis IIIA by intracerebrospinal fluid gene therapy. J Clin Invest 2013.
65. Tardieu M, Zerah M, Husson B, de Bournonville S, Deiva K, Adamsbaum C, et al. Intracerebral administration of adeno-associated viral vector serotype rh.10 carrying human SGSH and SUMF1 cDNAs in children with mucopolysaccharidosis type IIIA disease: results of a phase I/II trial. Hum Gene Ther 2014;25:506-16.
66. Roberts AL, Thomas BJ, Wilkinson AS, Fletcher JM, Byers S. Inhibition of glycosaminoglycan synthesis using rhodamine B in a mouse model of mucopolysaccharidosis type IIIA. Pediatr Res 2006;60:309-14.
67. Roberts AL, Rees MH, Klebe S, Fletcher JM, Byers S. Improvement in behaviour after substrate deprivation therapy with rhodamine B in a mouse model of MPS IIIA. Mol Genet Metab 2007;92:115-21.
68. Roberts AL, Fletcher JM, Moore L, Byers S. Trans-generational exposure to low levels of rhodamine B does not adversely affect litter size or liver function in murine mucopolysaccharidosis type IIIA. Mol Genet Metab 2010;101:208-13.
69. Piotrowska E, Jakobkiewicz-Banecka J, Baranska S, Tylki-Szymanska A, Czartoryska B, Wegrzyn A, et al. Genistein-mediated inhibition of glycosaminoglycan synthesis as a basis for gene expression-targeted isoflavone therapy for mucopolysaccharidoses. Eur J Hum Genet 2006;14:846-52.
70. Malinowska M, Wilkinson FL, Langford-Smith KJ, Langford-Smith A, Brown JR, Crawford BE, et al. Genistein improves neuropathology and corrects behaviour in a mouse model of neurodegenerative metabolic disease. PLoS One 2010;5:e14192.
71. Malinova V, Wegrzyn G, Narajczyk M. The use of elevated doses of genistein-rich soy extract in the gene expression-targeted isoflavone therapy for Sanfilippo disease patients. JIMD Rep 2012;5:21-5.
72. Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebicek M, et al. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 2000;355:1481-5.
73. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. Lancet Neurol 2007;6:765-72.
74. Guffon N, Bin-Dorel S, Decullier E, Paillet C, Guitton J, Fouilhoux A. Evaluation of miglustat treatment in patients with type III mucopolysaccharidosis: a randomized, double-blind, placebo-controlled study. J Pediatr 2011;159:838-44.e1.
75. Suzuki Y. Emerging novel concept of chaperone therapies for protein misfolding diseases. Proc Jpn Acad Ser B Phys Biol Sci 2014;90:145-62.
76. Feldhammer M, Durand S, Pshezhetsky AV. Protein misfolding as an underlying molecular defect in mucopolysaccharidosis III type C. PLoS One 2009;4:e7434.