Vol. 2 • No. 2 • October 2020

www.isgd.or.kr

eISSN 2671-6771

JIG

Journal of Interdisciplinary Genomics

Interdisciplinary Society of Genetic & Genomic Medicine

JIG Journal of Interdisciplinary Genomics

www.isgd.or.kr

eISSN 2671-6771

Vol. 2, No. 2, October 2020
Published in 31 October 2020

AIMS AND SCOPE

Journal of Interdisciplinary Genomics (*J Int Gen; JIG*) is an official publication of the Interdisciplinary Society of Genetic & Genomic Medicine. The journal is devoted to the dissemination the understanding of knowledge on the field of cytogenetics, molecular genetics, and clinical genetics through sharing of the latest scientific information.

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Publisher: **Chong Kun Cheon**
Published by **Interdisciplinary Society of Genetic & Genomic Medicine**
Editor-in-Chief: **Kyung Ran Jun**

Editorial Office: Interdisciplinary Society of Genetic & Genomic Medicine
Room 2002, 199 Megi-ro, Mulgeum-eup, Yangsan 50653, Korea
Tel: +82-55-366-7716, Fax: +82-55-360-2181, E-mail: jun@paik.ac.kr, Homepage: http://isgd.or.kr/

Printed by Academya Publishing Co.
Room 2003, Daerung Techno Town 15-Cha, 401 Simin-daero, Dongan-gu, Anyang 14057, Korea
Tel: +82-31-389-8811, Fax: +82-31-389-8817, E-mail: journal@academya.co.kr, Homepage: https://academya.co.kr/

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JIG Journal of Interdisciplinary Genomics

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JIG Journal of Interdisciplinary Genomics

https://doi.org/10.22742/JIG.2020.2.2.13
Journal of Interdisciplinary Genomics 2020;2(2):13-17

FRMD7-associated Infantile Nystagmus Syndrome

Kwang-Dong Choi[1], Jae-Hwan Choi[2]

[1]Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, Busan, Korea; [2]Department of Neurology, Pusan National University School of Medicine, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea

Infantile nystagmus syndrome (INS) is a genetically heterogeneous disorder. To date, more than 100 genes have been reported to cause INS and there is significant overlap in phenotypic characteristics. The most common form of X-linked INS is attributed to *FRMD7* at Xq26. Recent advances in molecular genetics have facilitated the identification of pathogenic variants of *FRMD7* and the investigation for underlying mechanisms of *FRMD7*-associated INS. This review summarizes genetic and clinical features of *FRMD7*-associated INS, and introduces updates on the pathogenesis of *FRMD7* mutation.

Key words: Infantile nystagmus syndrome, *FRMD7*

REVIEW

Received: September 3, 2020
Accepted: September 22, 2020

Correspondence to: Jae-Hwan Choi
Department of Neurology, Pusan National University School of Medicine, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, 20 Geumo-ro, Mulgum-eup, Yangsan 50612, Korea
Tel: +82-55-360-2122
Fax: +82-55-360-2152
E-mail: rachelbolan@hanmail.net

ORCID
Kwang-Dong Choi:
https://orcid.org/0000-0002-9373-4710
Jae-Hwan Choi:
https://orcid.org/0000-0002-4120-9228

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INTRODUCTION

Infantile nystagmus syndrome (INS), formerly called congenital nystagmus is characterized by rhythmic involuntary oscillations of the eyes that are present at birth or during infancy [1]. It can be associated with afferent visual system disorders such as ocular albinism, anterior segment dysgenesis, and foveal hypoplasia (Fig. 1). On the other hand, idiopathic INS arises independently of any other visual or neurological disorders. This has led to speculation that idiopathic INS may be caused by abnormal development of the ocular motor system itself rather than disorders of the afferent visual pathway [2,3].

The inheritance patterns of idiopathic INS are heterogeneous and have been reported as autosomal dominant, autosomal recessive, or X-linked trait [4-6]. However, the most common form of inheritance is X-linked, which can be dominant or recessive. Three loci have been identified at Xp11.4-p11.3, Xp22, and Xq26-q27, but approximately 50% of idiopathic INS families have been linked to Xq26-q27. After Tarpey et al. first identified pathogenic mutations in *FRMD7* (MIM#300628) at Xq26, over 90 different mutations have been reported in patients with idiopathic INS [7].

This review summarizes genetic and clinical features of *FRMD7*-associated INS, and introduces updates on the pathogenesis of *FRMD7* mutation.

FRMD7 (FERM Domain-Containing 7) Structure and Function

The *FRMD7* gene consists of 12 exons and encodes a 714-residue polypeptide [6]. It contains a conserved N-terminal FERM domain (amino acids 2-282) and FERM-adjacent (FA) domain (amino acids 288-336), whereas the C-terminal region has no significant homology to other proteins (Fig. 2A). The FERM domain has 3 lobed "cloverleaf" structures: F1 (lobe A), F2 (lobe B), and F3 (lobe C). These are plasma membrane-cytoskeleton coupling proteins which bind to actin

or other cytoskeleton components. The FA domain contains conserved motifs that are potential substrates for kinases, suggesting its regulatory effect in FRMD7 protein. In situ hybridization experiments in human embryonic brain showed FRMD7 expression in neuronal tissues involved in the vestibulo-ocular reflex and optokinetic reflex such as the developing

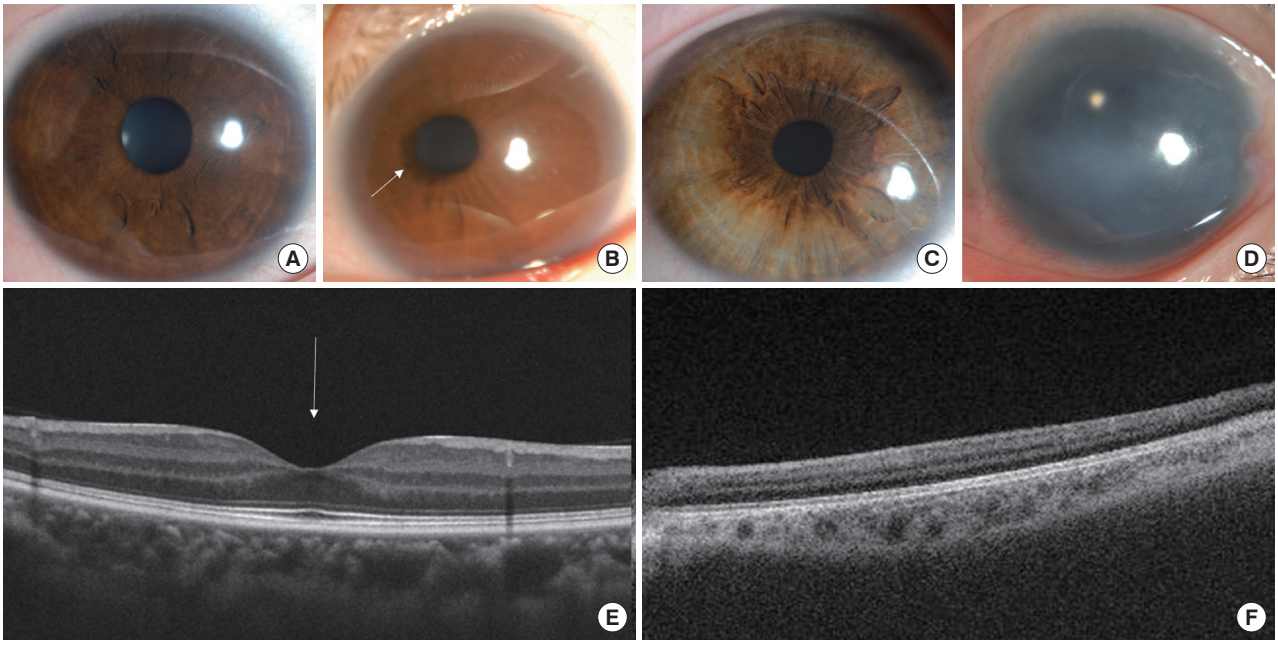


Fig. 1. Afferent visual system disorders associated with infantile nystagmus syndrome. (A) Anterior segment photography of normal eye. (B) Nasally displaced pupil with iris ectropion uvea (white arrow). (C) Iris hypopigmentation seen in ocular albinism. (D) Complete absence of the iris. (E) Optical coherence tomogram showing a normal foveal fit (white arrow). (F) Absence of foveal pit.

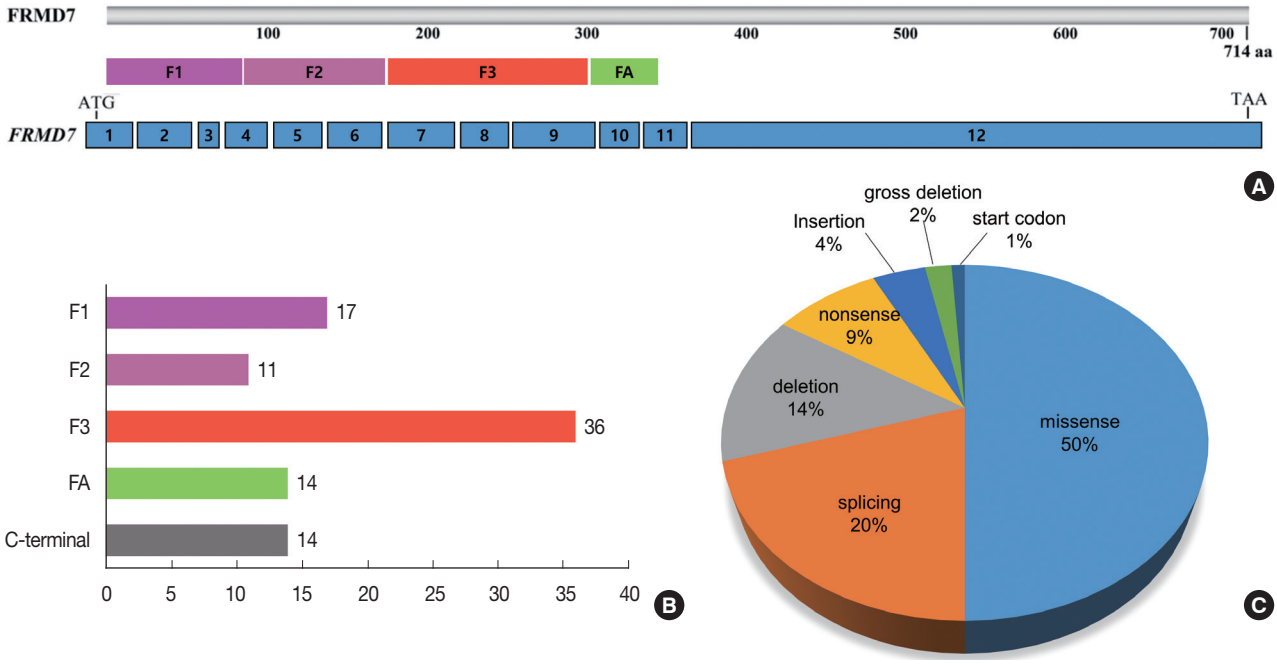


Fig. 2. (A) Schematic representation of FRMD7 protein. The FRMD7 protein contains an N-terminal FERM domain (F1, F2, and F3 lobes) and a FERM-adjacent (FA) domain. (B) Localization of *FRMD7* mutations. F3 lobe is the most mutation-rich domain. (C) Spectrum of *FRMD7* mutations. The missense mutation accounts for a half of all *FRMD7* mutations.

neural retina, optic stalk, otic vesicle, vestibulocochlear nerve, vestibular nucleus, and cerebellum [7-9].

The FRMD7 protein is highly co-localized with the actin of primary neurites in differentiating Neuro2A cells, which promotes elongation of axons and dendrites [10]. Knockdown of FRMD7 protein causes a reduction in average neurite length [11]. Several studies have proposed a mechanism of FRMD7 regulation for neuronal cytoskeletal dynamics. The FRMD7 protein shares close amino acid sequence homology with two other FERM domain containing proteins: FARP1 and FARP2 [6]. They are involved in neurite outgrowth and branching through activating Rho GTPase signaling. Rho GTPases are key regulators of the actin cytoskeleton in eukaryonic cells and mediate morphological changes during neuronal development and plasticity. It was found that wild-type human FRMD7 activated Rac1 signaling by interacting with RhoGDIα, the main regulator of Rho GTPase, while mutant FRMD7 failed to interact with RhoGDIα and to activate Rac1 signaling [12]. Recent studies also demonstrated that FRMD7 regulates the expression of Rac1 in stable SHSY-5Y cells [13], and mutant FRMD7 significantly influences the expression of Rac1, Cdc42, and RhoA during the induction period of human fibroblasts-reprogrammed neurons [14]. Thus, it is possible that FRMD7 is involved in the regulation of neuronal cytoskeletal dynamics through Rho GTPase signaling at the growth cone. Alternatively, the interaction between FRMD7 and calcium/calmodulin-dependent serine protein kinase (CASK) may promote the membrane extension during neurite outgrowth since the function of CASK is to link the plasma membrane to the actin cytoskeleton [15]. Furthermore, FRMD7 is specially localized in starburst cells of the mouse retina and the directional selective (DS) inhibitory input from starburst cells to DS ganglion cells is lost in FRMD7 mutant mice [16]. A recent study found FRMD7 to directly interact with the loop between transmembrane domains 3 and 4 of GABRA2, a type A gamma-aminobutyric acid (GABA) receptor subunit, and colocalization of FRMD7 and GABRA2 was found in the mouse retina [17]. Thus, *FRMD7* mutations perturb the interaction between FRMD7 and GABRA2, which may impair GABA inhibitory inputs from starburst cells to DS ganglion cells, eventually leading to the loss of optokinetic reflex that can be seen in INS patients. All of these findings support that nystagmus by *FRMD7* mutations may result from defective axogenesis, dendritogenesis, and neuronal guidance in the areas of the brain which control eye movements.

FRMD7 Mutations

To date, over 90 different mutations within *FRMD7* have been reported (Supplementary Table S1) [18,19]. Approximately 84% of mutations concentrates heavily within the N-terminal FERM and FA domain without any consistent hot spots (Fig. 2B). Most have been identified in single case with idiopathic INS, but some mutations including c.41delAGA (p.K14del), c.70G>A (p.G24R), c.875T>C (p.L292P), c.910C>T (p.R303X), and c.1003C>T (p.R335X) have been detected in different racial groups. Especially, c.875T>C (p.L292P) accounted for more than 50% of Korean patients carrying *FRMD7* mutations [19]. All patients with c.875T>C came from the same restricted region (Gyeongsangnam-do) of Korea, and shared two single-nucleotide polymorphisms (rs6637934, rs5977623) of exon 12 within *FRMD7*, suggesting that c.875T>C might have arisen from the founder effect in the Korean population with idiopathic INS.

A half of the mutations are missense which may destabilize the overall structure of FRMD7 protein, while the other half are predicted to cause gross defects at the protein level due to nonsense mutations, frameshift by small deletion or insertion, aberrant splicing, and large intragenic deletion (Fig. 2C). Among the 12 exons, exon 9 represents the most common mutation-rich exon (23%), followed by exon 12 (12%) and exon 8 (11%).

Incomplete penetrance was observed in female carriers, ranged from 30 to 100% [5,20-23]. This phenomenon has been explained by skewed X-inactivation and interactions with disease-modifying genes or environmental factors. Although skewed X-inactivation has consistently been suggested as a mechanism that may influence the penetrance of X-linked disorders in females, some studies have revealed that there was no clear causal link between X-inactivation pattern and phenotype in INS families with *FRMD7* mutation [20,21]. Furthermore, affected females showed random X-inactivation, reflecting a tissue mosaicism [22]. Different methylation patterns for the X chromosome were also found between female carriers, implying that a molecular basis for variable methylation might not be involved in the dissimilar penetrance [21]. Further investigations of X-inactivation status of *FRMD7* may help understand the incomplete pattern of inheritance.

Clinical Features of *FRMD7*-associated INS

The clinical features of *FRMD7*-associated INS are not much different from those of non-*FRMD7* INS. The nystagmus is present at birth or during infancy, and usually manifests as

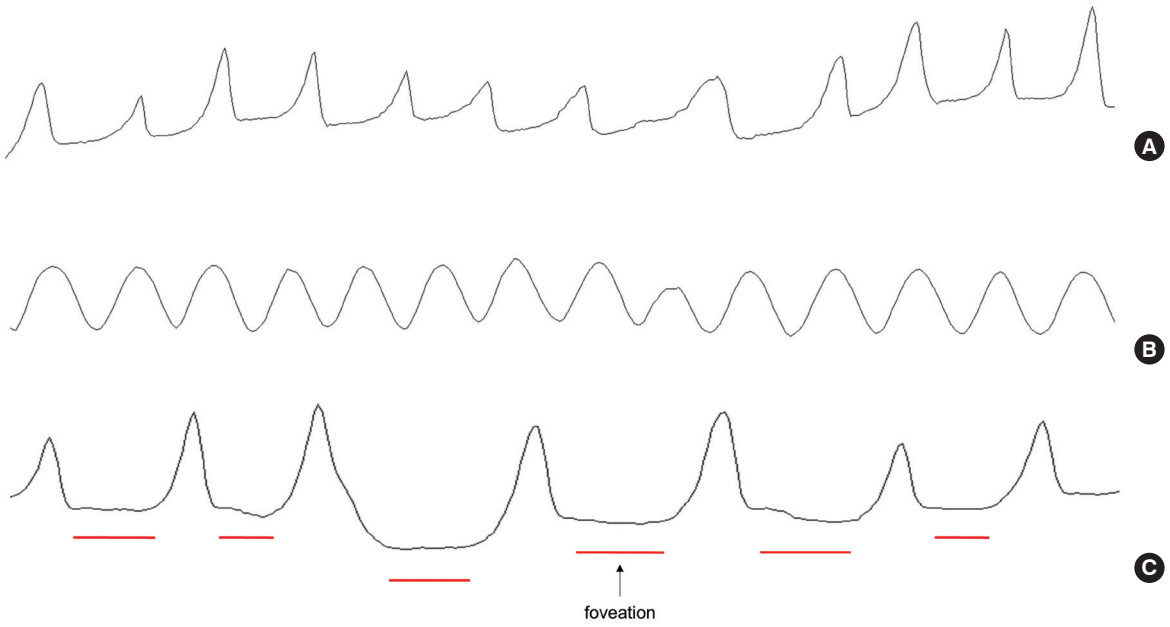


Fig. 3. Nystagmus waveforms recorded by video-nystagmography. (A) Jerk nystagmus with slow phases that drift away from the fixation position with increasing velocity waveforms. (B) Pendular nystagmus showing sinusoidal oscillations. (C) Foveation period (red bars) which the eye velocity is at or near zero.

horizontal conjugate oscillations, while vertical nystagmus is not typical for *FRMD7*-associated INS [1,4]. The direction of the nystagmus changes with eccentric gaze (right-beating on right gaze and left-beating on left gaze) or alternates periodically with time (periodic alternating nystagmus) [8,19]. The nystagmus is often accentuated by anxiety, attention, and attempts to fixate an object, while attenuated with eyelid closure or on convergence. The nystagmus waveform can be pendular or jerk with increasing exponential slow phases (Fig. 3A and 3B), but a pendular waveform is more common in adults with *FRMD7* mutations.

The nystagmus decreases when the eyes are moved into a particular position within the orbit, called the null point or zone [1]. Some individuals with INS tend to turn their head close to the null point or zone, resulting in abnormal head posture (AHP). The presence of AHP often leads parents to bring a child for medical evaluation and treatment.

Despite continuous eye oscillations, individuals with *FRMD7*-associated INS show relatively good visual acuity and no oscillopsia due to the presence of foveation period which the eye velocity is at or near zero (Fig. 3C). During this brief period, the image of the target is relatively stationary in the foveal area, leading to good visual acuity without oscillopsia [1]. Furthermore, *FRMD7*-associated INS is not accompanied with afferent visual system disorders causing reduced visual acuity such as foveal anomaly or retina dystrophy. Although previous studies have revealed morphological changes of retina and optic nerve such as decreased peripapillary retinal nerve fiber layer and shallow foveal pit and optic nerve head, these changes may be subclinical [9,18,19]. However, some individuals may complain of oscillopsia when the nystagmus is pronounced or the individual is tired.

CONCLUSION

FRMD7 is a major disease-causing gene of idiopathic INS. Although the molecular pathogenesis of *FRMD7* is still unclear, it is thought that *FRMD7* may participate in neuronal development in the areas of the brain controlling ocular motor and gaze stability. Further functional investigation and mutant analysis are needed to reveal the pathogenic mechanisms of *FRMD7*-associated INS.

ACKNOWLEDGMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2017R1D-1A3B03033237).

CONFLICTS OF INTEREST

The authors have no financial conflicts of interest.

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Supplementary Table S1. A list of the FRMD7 mutations reported in the literature

Domain	Exon	Nucleotide	Protein	Class	Origin	Reference
	1	c.1A>G	p.M1V	Start codon	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
F1	1	c.41delAGA	p.K14del	Deletion	England, China	Tarpey P. Nat Genet 2006; Zhang Q. Mol Vis 2007; Bai D. Sci China Life Sci 2017; Jia X. Mol Med Rep 2017
	1	c.47T>C	p.F16S	Missense	Russia, England, China	Gudzenko S. Genomic Med 2008; Thomas MG. Brain 2011; Wu S. J Mol Neurosci 2019
	1i	c.57+1G>A		Splicing	China	Jia X. Mol Med Rep 2017
	1i	c.57+5G>A		Splicing	Germany	Schorderet DF. Hum Mutat 2007
	1i	c.58-1G>A		Splicing	England	Thomas MG. Brain 2011
	2	c.58C>T	p.Q20*	Nonsense	Germany	Schorderet DF. Hum Mutat 2007
	2	c.70G>A	p.G24R	Missense	Ireland, China, England, Belgium, France	Tarpey P. Nat Genet 2006; Zhang Q.Mol Vis 2007; Thomas MG. Brain 2011; AlMoallem B, Invest Ophthalmol Vis Sci 2015; Michaud V. Ophthalmic Genet 2019
	2	c.70G>T	p.G24W	Missense	China	Li N. Mol Vis 2008
	2	c.71G>A	p.G24E	Missense	Austria	Tarpey P. Nat Genet 2006
	2i	c.162+2T>C		Splicing	China	Bai D. Sci China Life Sci 2017
	2i	c.162+5G>A		Splicing	England	Tarpey P. Nat Genet 2006
	2i	c.162+6T>C		Splicing	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
	2i	c.163-1G>T		Splicing	China	Hu Y. Mol Vis 2012
	3i	c.205+2T>G		Splicing	England	Tarpey P. Nat Genet 2006
	3i	c.206-1G>A		Splicing	China	Bai D. Sci China Life Sci 2017
	3i	c.206-5T>A		Splicing	England	Thomas MG. Hum Mol Genet 2014
F2	4	c.252G>A	p.V84=	Splicing	England	Tarpey P. Nat Genet 2006
	4	c.284G>T	p.R95M	Missense	China	Bai D. Sci China Life Sci 2017
	4i	c.284+1G>A		Splicing	England	Tarpey P. Nat Genet 2006; Self JE. Arch Ophthalmol 2007
	4i	c.285-118C>T		Splicing	England	Thomas MG. Hum Mol Genet. 2014
	6	c.425T>G	p.L142R	Missense	Ireland, America	Tarpey P. Nat Genet 2006; Shiels A. Mol Vis 2007
	6	c.436C>T	p.R146W	Missense	China	Zhang Q. Mol Vis 2007
	6	c.473T>A	p.I158N	Missense	China	Jia X. Mol Med Rep 2017
	6	c.479insT	p.H160Lfs*13	Insertion	England	Tarpey P. Nat Genet 2006
	6i	c.497+5G>A		Splicing	Belgium	AlMoallem B. Invest Ophthalmol Vis Sci 2015
	6i	c.498-2A>G		Splicing	America	Schorderet DF. Hum Mutat 2007
	6i	c.498-3C>T		Splicing	China	Yan N. BMC Med Genet 2019
F3	7	c.521A>T	p.D174V	Missense	China	Bai D. Sci China Life Sci 2017
	7	c.556A>G	p.M186V	Missense	India	Gupta S. Neurosci Lett 2015
	7	c.575A>C	p.H192P	Missense	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
	7	c.580G>A	p.A194T	Missense	China	Jiang L. Invest Ophthalmol Vis Sci 2020
	7	c.580G>T	p.A194S	Missense	China	Jia X. Mol Med Rep 2017
	7	c.586G>A	p.D196N	Missense	China	Bai D. Sci China Life Sci 2017
	7	c.601C>T	p.Q201*	Nonsense	Italy-Germany	Tarpey P. Nat Genet 2006
	7	c.605T>A	p.I202N	Missense	China	Jia X. Mol Med Rep 2017
	7	c.623A>G	p.H208R	Missense	China	Li N. Mol Vis 2011
	7i	c.645+1G>C		Splicing	Madagascar	Tarpey P. Nat Genet 2006
	8	c.657G>T	p.K219N	Missense	Russia	Gudzenko S. Genomic Med 2008
	8	c.660del	p.N221Ifs*11	Deletion	Belgium	AlMoallem B. Invest Ophthalmol Vis Sci 2015
	8	c.A661G	p.N221D	Missense	England	Tarpey P. Nat Genet 2006
	8	c.673T>G	p.W225G	Missense	Switzerland	Schorderet DF. Hum Mutat 2007
	8	c.676G>A	p.A226T	Missense	England	Tarpey P. Nat Genet 2006
	8	c.685C>T	p.R229C	Missense	China	Zhang Q. Mol Vis 2007; Bai D. Sci China Life Sci 2017
	8	c.685C>G	p.R229G	Missense	Turkey	Kaplan Y. Br J Ophthalmol 2008
	8	c.691T>G	p.L231V	Missense	Ireland-Germany	Tarpey P. Nat Genet 2006; Thomas MG. Brain 2011
	8	c.694_695delAG	p.S232Ffs*2	Deletion	China	Li N Mol Vis 2008

(*Continued to the next page*)

Supplementary Table S1. Continued

Domain	Exon	Nucleotide	Protein	Class	Origin	Reference
	8	c.719T>C	p.I240T	Missense	China	Zhu Y. Sci Rep 2013
	8	c.722A>G	p.K241R	Missense	Korea	Choi JH. Invest Ophthalmol Vis Sci 2018
	9	c.766T>A	p.F256I	Missense	China	Bai D. Sci China Life Sci 2017
	9	c.780C>A	p.S260R	Missense	China	Zhang X. Sci Rep 2014
	9	c.781C>G	p.R261G	Missense	China	Zhang B. Mol Vis 2007;Zhao H. BMJ Open 2016
	9	c.782G>A	p.R261Q	Missense	China	Li N. Mol Vis 2008; Bai D. Sci China Life Sci 2017
	9	c.G796C	p.A266P	Missense	England	Tarpey P. Nat Genet 2006
	9	c.801C>A	p.F267L	Missense	Belgium	AlMoallem B. Invest Ophthalmol Vis Sci 2015
	9	c.804G>T	p.W268C	Missense	Russia	Gudzenko S. Genomic Med 2008
	9	c.805A>C	p.K269Q	Missense	China	Wang Z. Acta Biochim Biophys Sin 2019
	9	c.811T>C	p.C270R	Missense	China	Bai D. Sci China Life Sci 2017
	9	c.811T>A	p.C271S	Missense	England	Thomas MG. Brain 2011; Jia X. Mol Med Rep 2017
	9	c.812G>A	p.C271Y	Missense	Scotland	Tarpey P. Nat Genet 2006; Thomas MG. Brain 2011
	9	c.812G>T	p.C271F	Missense	China	He X. Mol Vis 2008; Li N. Mol Vis 2008
	9	c.814G>T	p.V272L	Missense	China	Li ND. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2008
	9	c.823_829delACCCTAC	p.T275fs	Deletion	China	Chen J. BMC Med Genet 2019
	9	c.824A>C	p.H275P	Missense	America	Schorderet DF. Hum Mutat 2007
FA	9	c.875T>C	p.L292P	Missense	Belgium, Korea, Japan	AlMoallem B. Invest Ophthalmol Vis Sci 2015; Choi JH. Invest Ophthalmol Vis Sci 2018; Kohmoto T. Hum Genome Var 2015
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	9	c.886G>T	p.G296C	Missense	China	Xiu Y. Mol Med Rep 2018
		c.887delG	p.G296Vfs*23	Deletion	Austria	Tarpey P. Nat Genet 2006
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JIG Journal of Interdisciplinary Genomics

https://doi.org/10.22742/JIG.2020.2.2.20
Journal of Interdisciplinary Genomics 2020;2(2):20-25

Mucopolysaccharidosis Type III: review and recent therapies under investigation

Jun Hwa Lee

Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

Mucopolysaccharidosis type III (MPS III or Sanfilippo syndrome) is a multisystem lysosomal storage disease that is inherited in an autosomal recessive manner. It consists of four subtypes (MPS IIIA, B, C, and D), each characterized by the deficiency of different enzymes that catalyze the metabolism of the glycosaminoglycan heparan sulfate at the lysosomal level. The typical clinical manifestation of MPS III includes progressive central nervous system (CNS) degeneration with accompanying systemic manifestations. Disease onset is typically before the age of ten years and death usually occurs in the second or third decade due to neurological regression or respiratory tract infections. However, there is currently no treatment for CNS symptoms in patients with MPS III. Invasive and non-invasive techniques that allow drugs to pass through the blood brain barrier and reach the CNS are being tested and have proven effective. In addition, the application of genistein treatment as a substrate reduction therapy is in progress.

Key words: MPS III, Sanfilippo syndrome, blood brain barrier, Treatment, Genistein

REVIEW

Revised: October 3, 2020
Accepted: October 13, 2020
Pulished: October 31, 2020

Correspondence to: Jun Hwa Lee
Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158 Paryong-ro, Masanhoewon-gu, Changwon 51353, Korea
Tel: +82-55-233-5931
Fax: +82-55-233-5359
E-mail: ljh3643@hanmail.net

ORCID
Jun Hwa Lee: https://orcid.org/0000-0001-9717-3677

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INTRODUCTION

Mucopolysaccharidosis type III (MPS III or Sanfilippo syndrome) is an autosomal recessive, multisystem lysosomal storage disease that is characterized by progressive central nervous system (CNS) degeneration manifested in the form of severe intellectual disability, developmental regression, autism spectrum disorder, behavioral problems, and sleep disturbances, with death usually in the mid-teens to early twenties [1]. Accumulation of glycosaminoglycans (GAGs) in the CNS can seriously affect neurons, leading to death through apoptosis or necrosis during the advanced stages of the disease [2]. The incidence of MPS III is estimated to be 1 in 70,000 live births, while the overall point prevalence varies with geographical area, but is estimated to be 1 to 9 in 1,000,000 people [3]. MPS III consists of 4 subtypes (MPS IIIA to D), each characterized by the deficiency of different enzymes that catalyze the metabolism of the GAG heparan sulfate (HS) at the lysosomal level (Table 1).

The prevalence of MPS varies with geographical area and certain subtypes appear to be predominant in specific regions of the world. Overall, MPS III types A and B are more commonly diagnosed than types C and D. The estimated incidences for subtypes MPS IIIA, IIIB, IIIC, and IIID are 1:100,000, 1:200,000, 1:1,500,000, and 1:1,000,000, respectively [1,3,4]. Although formal diagnostic criteria for MPS III have not been established yet, the condition can be suspected based on clinical findings and supportive laboratory or imaging findings. Clinical findings may include symptoms such as coarse facies, thick hair and hirsutism, hepatosplenomegaly, joint stiffness, language and motor delays, behavioral prob-

lems including hyperactivity and aggressive or defiant behaviors, hearing loss, sleep disturbances, intellectual disability, seizure, and progressive developmental regression. Fig. 1 shows serial photographs, according to age, of my patient with MPS IIIB [5].

Table 1. The genes and enzymes associated with each MPS III subtypes

Subtype	Gene	Deficient enzyme	Locus
MPS IIIA	*SGSH*	N-sulphoglucosamine sulphohydrolase	17q25.3
MPS IIIB	*NAGLU*	Alpha-N-acetylglucosaminidase	17q21.2
MPS IIIC	*HGSNAT*	Heparan-alpha-glucosaminide N-acetyltransferase	8q11.21
MPS IIID	*GNS*	N-acetylglucosamine-6-sulfatase	12q14.3

Supportive laboratory findings include an abnormality in either quantitative or qualitative GAG analysis, while imaging findings include a skeletal survey revealing mild signs of dysostosis multiplex such as thickened 'oar-shaped' ribs, scoliosis, kyphosis, misshaped or hypoplastic vertebral bodies, thickened diploic space, etc. The diagnosis of MPS III is established as either biallelic pathogenic variants in one of four genes (*GNS*, *HGSNAT*, *NAGLU*, and *SGSH*) or identification of deficiency of the respective lysosomal enzymes [1].

There is still no definitive treatment for the CNS symptoms of MPS III. The most difficult problem in treating neurological symptoms in MPS III patients is getting the drug into the brain, in other words, overcoming the blood brain barrier (BBB). Extensive research is being carried out on this problem.



Fig. 1. Serial photographs of a patient with MPS IIIB. (A) Mild facial coarseness was noted at the age of 4 years. Facial dysmorphism, including coarse facial features, a depressed nasal bridge, prominent eyebrows, and malocclusion, was apparent at the ages of (B) 13 and (C) 18 years. (D) He was bedridden and malnourished at the age of 21 years.

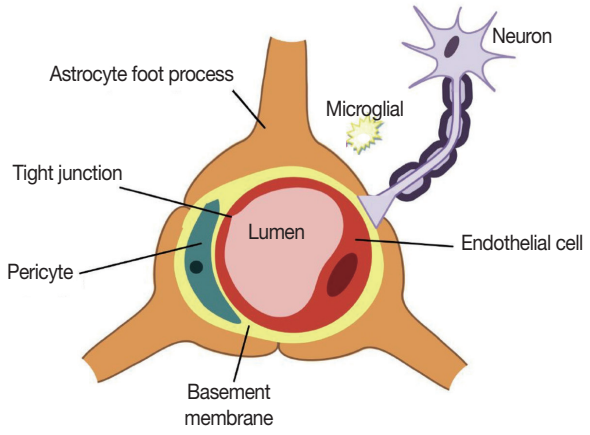


Fig. 2. Angioarchitecture of the blood brain barrier (BBB). BBB consists of a complex system of endothelial cells, astrocyte foot processes, pericytes, microglia, and neurons.

Table 2. Techniques for brain drug delivery

Invasive techniques
Blood–brain barrier transient disruption
Intracerebroventricular and intrathecal infusion
Non-invasive techniques
Modification of the drug to enhance its lipid solubility
Use of transport/carrier systems
Inhibition of efflux transporters that impede drug delivery
Trojan horse approach
Chimeric peptides
Monoclonal antibody fusion proteins
Pro-drug bioconversion strategies
Nanoparticle-based technologies
Gene therapy
Intracerebral gene therapy
Intranasal drug delivery
Substrate reduction therapy

This review describes possible strategies to overcome the BBB and recent therapies under investigation for MPS III.

The structure of BBB and transport through the BBB

The BBB is a semi-permeable membranous barrier that is located at the interface between the blood and cerebral tissue. It consists of a complex system of endothelial cells, astrocyte foot processes, pericytes, microglia, and neurons (Fig. 2).

In general, the BBB allows the passage of only lipophilic molecules with a low molecular weight (under 400-600 Da) and with a positive charge. Other molecules require certain cell endogenous transport systems, such as carrier-mediated, receptor-mediated or absorption-mediated transport. Commonly, there are five basic mechanisms by which solute molecules move across membranes: 1) simple or passive diffusion, e.g., blood gases, anesthetics, and heroin, 2) solute carriers, which constitute a superfamily of membrane transport proteins, e.g., glucose, amino acids, nucleosides, monocarboxylates, organic anions and cations, and L-3,4-dihydroxyphenylalanine 3) carrier-mediated efflux (efflux transporters), these ATP-binding cassette transporters use ATP hydrolysis to pump molecules across the membrane and therefore they can force the efflux of solutes against a concentration gradient. e.g., P-glycoprotein (Pgp:ABCB1) and breast cancer-related protein (BCRP:ABCG2) 4) receptor-mediated transcytosis, e.g., iron, insulin, and leptin, and 5) diapedesis of mononuclear leukocytes. Once the leukocytes enter the brain, they become microglia, which are cells with the brain's immune capabilities [1,6]. It has been estimated that more than 90% of all small-molecule drugs and nearly 100% of all larger therapeutics are not able to overcome the BBB [7]. Therefore, a lot of research effort is required to develop a new strategy that can effectively surpass the BBB and deliver therapeutic products into the CNS. The strategic treatment approaches to bypass the BBB can be categorized as invasive or non-invasive techniques (Table 2).

Techniques for brain drug delivery

Invasive techniques

- **BBB transient disruption:** This technique uses noxious agents, hyperosmotic solutions or ultrasound (mannitol, dimethyl sulphoxide, ethanol, metals, glycerol and polysorbate-80, X-irradiation, etc.) to shrink the brain's endothelial cells by breaking down tight junctions, thus allowing various molecules to enter the cerebral tissue.
- **Intracerebroventricular and intrathecal infusion:** This technique uses injection or intraventricular infusion of therapeutic proteins directly into the cerebrospinal fluid (CSF). Animal studies on MPS IIIA show that continual infusion of replacement enzyme partially ameliorates clinical, histological, and biochemical aspects in MPS IIIA mice, when treatment begins at an early symptomatic stage [8]. Clinical trials with the same technique have been initiated in humans. Recombinant human heparan-N-sulfatase (rhHNS) administration via implanted intrathecal drug delivery device in twelve patients with MPS IIIA was found to be generally safe and well tolerated. The treatment resulted in a consistent decline of HS in the CSF, suggesting *in vivo* activity in the relevant anatomical compartment [9].

Non-invasive techniques

- **Modification of the drug to enhance its lipid solubility:** This technique involves chemical transformation of water-soluble molecules into lipid-soluble molecules that are capable of crossing the BBB [10].
- **Use of transport/carrier systems:** This technique involves chemical modification of small-molecule therapeutic drug to enable the use of endogenous transport/carrier systems that mimic the structure of related specific endogenous molecules. Glucose transporter type 1, large neutral amino-acid transporter type 1, cationic amino-acid transporter type 1, monocarboxylic acid transporter type 1, and equilibrative nucleoside transporter 1 are some of the most common endogenous carrier-mediated BBB transporters used as carrier systems for drug delivery [11].
- **Inhibition of efflux transporters that impede drug delivery:** This technique involves the pharmacological inhibition of select efflux transporters that prevent blood-to-brain drug uptake, examples of which include P-glycoprotein, breast cancer resistance protein (BCRP in humans and Bcrp in rodents), and multidrug resistance proteins (MRPs in humans and Mrps in rodents), etc. Among substrates transported by BCRP/Bcrp are chemotherapeutic agents (i.e., mitoxantrone), anthracyclines (i.e., etoposide and teniposide), and campothecin derivatives (i.e., topotecan and irinotecan). Transport of etoposide, cisplatin, and doxorubicin has been demonstrated though MRP6/Mrp6 [2,6].
- **Trojan horse approach:** This technique uses molecules such as endogenous ligands or monoclonal antibodies that, while acting as molecular 'trojan horses', bind exofacial epitopes on BBB receptor-mediated transport systems, thus triggering internalization of the receptor and the attached drug. This technique is being used to ferry drugs, proteins, and non-viral gene medicines across the BBB [2, 6].
- **Chimeric peptides:** This technique is being used for the transport of therapeutic compounds that can only be transported at very low rates through the BBB. The technique enables brain penetration by redesigning biological drugs into monoclonal antibody fusion proteins (IgG fusion proteins). Research to evaluate the efficacy of this technique is being conducted in mouse models of neurological disorders, including Parkinson's disease, stroke, Alzheimer's disease, and lysosome storage disorders [7].
- **Pro-drug bioconversion strategies:** This technique consists of developing pro-drug compounds (also called pro-agents), which are therapeutically inactive agents that can cross the BBB and enter into the brain parenchyma. Upon reaching the target site, these compounds undergo enzymatic and/or chemical transformations and modify their structure, resulting in a biologically active form that is capable of exerting the desired pharmacological effect [12].
- **Nanoparticle-based technologies:** This technology is primarily based on the use of nanoscale technology for drug release in the brain; the delivery system uses a variety of nanoscale drug delivery platforms, including primarily lipid and polymer-based nanoparticles (NPs) [13]. Studies have shown the potential of NPs as effective drug carriers. SFor example, a study tested the effectiveness of laronidase surface-functionalized lipid-core nanocapsules for the treatment of MPS I; another study loaded arylsulfatase B onto poly(butyl cyanoacrylate) NPs to affect neurological manifestations such as spinal cord compression in MPS VI by delivery of the therapeutic enzyme across the BBB; a third study in two murine models of MPS I and MPS II aimed at assessing the g7-NP brain delivery capacity using a model drug (Albumin-fluorescein isothiocyanate conjugate) [14-16].
- **Gene therapy:** This technique consists of transferring recombinant DNA with therapeutic function directly into the cells of specific organs [17]. It is a promising solution for neurodegenerative conditions where the neuropathology has spread throughout the entire brain, thus requiring a global CNS gene delivery for effective treatment. Two types of applications of gene therapy are possible: '*ex vivo*', which involves the collection of target cells, treatment with genetic engineering techniques, and reinjection into the patient; and '*in vivo*', which is the delivery of a gene directly into the body through a suitable vector such as a plasmid or a non-pathogenic viral vector [retrovirus, adenovirus, adeno-associated virus (AAV)]. Extensive studies of intravenous vector administration performed in newborn mice models of MPS I and MPS VII have shown encouraging results [18]. In another study, the use of systemic delivery AAV vectors in murine models of MPS I, IIIA, IIIB, and VI has demonstrated a reduction of the corresponding substrate in the CNS [19].
- **Intracerebral gene therapy:** This technique involves direct viral gene delivery into the brain parenchyma or ventricular system. A variety of non-neuronal viral vectors have been studied for CNS gene transfer *in vivo* in the brain of MPS I, MPS IIIA, MPS IIIB, and MPS VII mouse models via

AAV, adenovirus, and lentivirus. The results of phase I/II clinical trials carried out to evaluate the feasibility and safety of brain injection of AAV vectors for MPS IIIA and IIIB suggest that intraparenchymal delivery may be a realistic option for neuropathic MPS [20].

- **Intranasal drug delivery:** This technique allows rapid delivery of therapeutic molecules directly to the CNS within minutes by bypassing the BBB via a neural pathway connecting the nasal mucosa and brain [21]. Lipid-based NPs have been studied for intranasal drug delivery and this non-invasive strategic approach has been used to evaluate the therapeutic efficacy of neurological symptoms in MPS I disease. In laboratory experiments in mice, intranasal administration of an α-L-iduronidase-encoding AAV serotype 9 (AAV9) vector resulted in the diffusion of the enzyme to deeper areas of the brain and related reduction of tissue GAG storage materials in the brain [22].

Substrate reduction therapy: genistein (4',5,7-trihydroxyisoflavone)

Genistein is a natural isoflavone that occurs in many plants and is known to have a variety of biological activities, from serving as a plant estrogen to displaying antioxidant activity [23]. Genistein is an inhibitor of tyrosine-specific protein kinases. Genistein-mediated reduction in the synthesis of HS is mediated through the inhibition of epidermal growth factor receptors and other growth factor receptors that regulate the transcription of genes involved in HS synthesis. In addition, *in vitro* studies have also revealed anti-inflammatory effects of genistein on nerve cells [24]. There are several studies that have identified genistein as an effective treatment for MPS III. Genistein has been shown to effectively inhibit HS synthesis in cultured fibroblasts of patients [9]. In another report, continuous administration of high-dose genistein to MPS IIIB mice for 9 months caused a significant reduction in lysosomal storage, HS substrate, and neuroinflammation in the cerebral cortex and hippocampus, resulting in correction of the behavioral defects observed [25]. Piotrowska *et al.* [26] reported that in eight pediatric patients with Sanfilippo disease, treatment with genistein-rich soy isoflavone extract showed possible positive effects on inhibition or slowing down of behavioral and cognitive problems. de Ruijter *et al.* [27] reported that in thirty MPS III patients administered genistein-rich soy isoflavone extract, there was an effective reduction in urinary excretion of GAGs and plasma HS concentration.

Studies on MPS III are actively underway

In MPS IIIA patients, these include a phase IIb study involving intrathecal rhHNS [9], intravenous delivery of a chemically modified sulfamidase in MPS IIIA mice [28], a phase II/III study involving AAV10, and a phase I/II study involving AAV9. In MPS IIIB patients, a phase I/II study involving tralesinidase Alf, a phase II/III study involving anakinra (kineret), and a phase I/II study involving AAV9 and AAV5 are ongoing.

CONCLUSIONS

MPS III is a multisystem lysosomal storage disease that presents progressive CNS degeneration with no currently available treatment for the CNS symptoms. Recently, many studies have been conducted on the treatment of the CNS symptoms. Invasive and non-invasive technique strategies that allow drugs to pass through the BBB and reach the CNS are being tested and have proven effective. In addition, the application of genistein treatment as a substrate reduction therapy is currently in progress. Thus, a possible treatment for CNS symptoms of MPS III is expected in the future.

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JIG Journal of Interdisciplinary Genomics

eISSN 2671-6771

Information Authors

Revised, 2nd: May 1, 2020

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The JIG follows the recommendations for authorship by the ICMJE, 2019 (http://www.icmje.org/icmje-recommendations.pdf) and Good Publication Practice Guidelines for Medical Journals 3rd Edition (KAMJE, 2019, https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13&per_page=). Authorship credit must be based on 1) substantial contributions to the concept and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors must meet the above four conditions.

A corresponding author should be designated when there are two or more authors. The corresponding author is primarily responsible for all issues to the editor and audience. Any comment of the corresponding author is regarded as opinion of all coauthors.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.

6. Originality and duplicate publication

All submitted manuscripts should be original and should not be considered by other scientific journals for publication at the same time. No part of the accepted paper should be duplicated in another scientific journal without permission by Editorial Board. If duplicate publications related to the papers of this journal are detected, sanctions against authors range from requesting their institutions to assess the facts, requesting a Letter to the Editor-in-Chief acknowledging the error and voluntarily withdrawing a paper, to a ban on publication in JIG up to 3 years.

7. Sex and gender equity in research

We encourage the use of the Sex and Gender Equity in Research (SAGER) guidelines (http://doi.org/10.1186/s41073016-0007-6) for reporting of sex (biological factor) and gender (identify, psychosocial or cultural factors) information in study design, data analysis, and manuscripts writing.

MANUSCRIPT PREPARATION AND FORMAT

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- Original articles
- Review article
- Editorial
- Brief report
- Image
- Letters to the editor

The other form could be submitted under the approval of the editorial board.

1. General principles

1) Manuscripts should be prepared using MicroSoft Word (.doc). All portions of the manuscript should be double-spaced with the font size of 12 with 3-cm blank margin in both sides, top and bottom of A4-sized paper (21 × 30 cm). The numbers on each page of the manuscript should be placed at the center of the bottom in a sequential manner starting from the title page.
2) Manuscripts should be submitted in English. Medical terminology should be written based on the most recent edition of English-Korean Korean-English Medical Terminology, published by the Korean Medical Association.
3) Acronyms should only be used when absolutely necessary for clarity. In cases in which the use of acronyms is desirable due to the repetition, the acronym should be expressed in a parenthesis when the corresponding terminology first appears in the manuscript.
4) Laboratory measurements should be used in International System of Units (SI) units. However, in some cases, non-SI units (conventional units) can also be used in a versatile manner. But the usage of units should be consistent.
5) The manuscript should be arranged in the following order: title page, abstract and keywords, main text (introduction, methods, results anddiscussion), conflicts of interest, acknowledgments, references, tables and figures.
6) All authors are encouraged to provide Open researcher and contributor ID (ORCID). Additional information about ORCID is available at http://orcid.org/.

2. Original articles

Title page and abstract

1) The title page should be as follows: the title of the manuscript, a short running title less than 50 characters, names of all authors and their current affiliations. In cases in which the authors belong to multiple affiliations, the affiliations during the study being reported should be matched to the authors' names using a superscript of Arabic numerals
2) The title of the manuscript should be no longer than 20 English words. The first letter of each word of the title must be capitalized. Acronyms should not be used in title except for special situations.
3) At the bottom of the title page, the corresponding author's name, address, and e-mail address should be indicated.
4) Provide the word count for the text only, excluding abstract, acknowledgments, figure legends, and references.
5) The number of figures and tables should be provided in the title page.
6) The word count for the abstract should be no more than 250 words, consisting of four sections: Background, Meth-

ods, Results, and Conclusion.

7) Three to 10 keywords relevant to the content of a manuscript should be attached after the abstract. In principle, the keywords should be found in MeSH terms of the Index Medicus (http://www.nlm.nih.gov/mesh/MBrowser.html).
8) Author names and affiliations: On the title page, write Each author's name (first name, middle name, and family name) followed by the highest academic degree, full institutional mailing addresses and ORCID (Open Researcher and Contributor ID) number. Each author on the list must have an affiliation. The affiliation includes department, university, or organizational affiliation and its location, including city, state/province (if applicable), and country. Authors have the option to include a current address in addition to the address of their affiliation at the time of the study. The current address should be listed in the byline and clearly labeled "current address." At a minimum, the address must include the author's current institution, city, and country. If an author has multiple affiliations, enter all affiliations on the title page.

Main text

1) ***The main text should be structured as Introduction, Methods, Results, and Discussion.*** Use headings and subheadings in the Methods section and Results section. Every reference, figure, and table must be cited numerically in the order mentioned in the text.
2) ***Introduction:*** Present the research purpose briefly and clearly, together with only the background information that is relevant to the purpose
3) ***Methods:*** Materials, methods, and study design should be presented in detail. In experimental research, methods should be described in such a manner that the experiments can be reproduced by the readers. A statement concerning IRB approval and consent procedures must appear at the beginning of the Methods section. The description for the reagents, kits machines used in the experiment should be precise with full descriptions for the kit number, company name, city and the country of its origin.
4) ***Results:*** A detailed description of the study results should be clearly arranged in a logical manner. In cases in which tables are used, the contents described in tables should not be redundantly described in the main text, but the important trends and points should be emphasized. Insertion of references with previously published data is not allowed in results section. Description of previously reported data or personal opinion should be mentioned in discussion section. In tables, figures, virgule constructions and within parentheses, 'minute' should be described with 'min' and 'hour with 'hr', and no 's' should be added to them
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Conflicts of interest

Any potential conflict of interest relevant to the manuscript is to be described. If there are no conflicts of interest, authors should state that none exist.

Acknowledgments

The acknowledgments should be presented after the main text and before the reference list. Acknowledgments should contain brief statements of assistance, financial support, and prior publication of the study in abstract form, where applicable. Any other matters associated with research funds, facilities and drugs which were used in the current manuscript should also be given in the Acknowledgments

References

1) References should be listed in the sequence cited in the paper, and sequential numbers should be attached in the middle or at the end of the corresponding sentences in the body of the text. The reference list should be given at the end of the document, after the main text and acknowledgments (if applicable) and before the tables.

   Original articles are limited to 40 references. Reference numbers in the text should appear in chronological order in normal type and in square brackets, e.g., "In the study by Norton et al. [23]…".
2) The names of all authors must be listed by the last name and the initials of first and middle names in each reference. List all authors when the number of authors is 6 or less. If 7 or more, list the first 6 authors and add "et al." Inclusive page numbers must be provided. The notation of academic journal names should be used with acro-

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3) All the references should be described in the following format:

Journals: authors' names (list the first 6 authors and add "et al."), title, journal name, year, volume, and page number

e.g., Amos-Landgraf JM, Ji Y, Gottlieb W, Depinet T, Wandstrat AE, Cassidy SB, et al. Chromosome breakage in the Prader-Willi and Angelman syndromes involves recombination between large, transcribed repeats at proximal and distal breakpoints. Am J Hum Genet 1999;65:370-86.

Book: authors' name(s), title, number of editions, place of publication, publisher, year of publication, and page numbers.

e.g., Imura H. The pituitary gland. 2nd ed. New York: Raven Press; 1974. p. 453-90.

Chapter in a book: authors' name(s), title, number of editions, place of publication, publisher, year of publication, chapter number and title, and page numbers.

e.g., Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. Chapter 29, Endometriosis; p. 1103-33.

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e.g., Kaplan SJ. Post-hospital home health care: the elderly's access and utilization [dissertation]. [St. Louis]: Washington University; 1995.

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Tables

1) Tables should be double-spaced and inserted on a separate page at the end of the text document, with the table number, table title and legend given above the table.
2) Titles of tables should be concise using a phrase and a clause. The first letter of each word of the title should be capitalized.
3) The numbers should be allocated accordingly in order in which the table was quoted in the main text.
4) For acronyms, provide the full names below the corresponding table. Symbols should be marked with small alphabet letters in the order of its usage, such as, a, b, c, d, e with their respective descriptions in the footnote.
5) Tables should be easy to understand while functioning independently.
6) Unnecessary longitudinal lines should not be drawn. Horizontal lines should be refrained from being used as much as possible

Figures and figure legends

1) Submit the figures separately from the main text. The resolution power of the pictures and photographs is expected to exceed 300 dpi. Figures should be included with online submissions, either as JPEG, GIF, TIFF, BMP, PICT with RTF manuscripts or embedded in the PDF file.
2) If two or more figures require the same number, Arabic numerals should be followed by letters (e.g., Fig. 1A, Fig. 1B).
3) An author may request pictures to be printed in color, but the cost of this will be charged to the author.
4) Assign sequential numbers (Arabic numerals) in the order referenced in the paper.
5) Figures legends should be written at the end of the manuscript, should be described with complete sentences rather than incomplete phrases or a clause. The expansions for the abbreviations used within the figure should be placed in the legend.
6) For microphotographs, describe the dyeing method and magnification ratio.
7) The description of footnotes below the figure should follow the order of that of acronyms and then symbols. Symbols should be marked with small alphabet letters in the order of its usage, such as, a, b, c, d, e, in superscript.

Supplemental data

Nonessential tables and figures may accompany articles as

online-only supplemental files. All online-only supplementary files should be combined in one document file (whenever possible) and uploaded separately during the submission process. This file must be clearly labeled as "Online-Only Supplemental Material." In addition, supplemental onlineonly files must be referenced in the main text of the manuscript at least once (e.g., "Supplemental Table S1").

All online-only supplemental files are subject to review, but such files will not be copyedited or proofread by EnM production staff. As such, authors are encouraged to review their supplemental files carefully before submitting them.

Lists that include names of principal investigators or writing groups may also be submitted as online-only supplements if they exceed 150 words. Otherwise, the names of principal investigators or writing groups should be listed in an appendix at the end of the main document, before the references.

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A review article is a review focusing on a specific title and commissioned by the Publication Committee for publishing. Manuscripts submitted as review articles will be subjected to the same review process as original research articles. Instructions for original articles should be followed for review articles. A review article should include an abstract not exceeding 200 words, for which the number of references should not exceed 60.

4. Editorial

Editorials are commissioned for the purpose of commenting on a specific paper published by the journal, not to reflect the views of the Society. There is no limitation on the format. But an editorial should be written in no more than four pages (A4) with the number of references limited to 20.

5. Brief report

Short communications of original research are published as case report. The purpose of the category is to permit publication of very important, high-quality mechanistic studies that can be concisely presented. These manuscripts should include a short nonstructured abstract (150 words maximum), Introduction, Methods, Results, and Discussion.

The total manuscript length should not exceed 1,200 words, excluding references and abstract. Brief reports can include a maximum of 20 references and two figures or tables.

6. Image

Images that may help make clinical decisions while being interesting and educational in terms of the treatment of endocrinology and metabolism should be prepared with a manuscript. The manuscript should not be more than one page (A4), with the number of references limited to five.

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A letter should contain constructive criticisms or comments on a specific paper published by the journal within the previous 6 months. The manuscript should be no more than one page (A4), with the number of references limited to five

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2) Submitted manuscripts are first reviewed by journal editors. If a manuscript fails to comply with the submission guidelines or the checklist (JIG Submission Checklist), it will be rejected for review and then returned to the author, to be re-written and re-submitted according to the submission guidelines.
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1) If it is necessary to revise a manuscript, the Publication Committee may do so insofar as it does not impact the original text, and according to its editing policy on wording and formats.
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Kyung Ran Jun, M.D, Ph.D.
Department of Laboratory Medicine, University of Inje,
875 Haeun-daero, Haeundae-gu, Busan 48108, Korea
E-mail: jun@paik.ac.kr

JIG Journal of Interdisciplinary Genomics

eISSN 2671-6771

Information Authors

Revised, 2nd: May 1, 2020

STUDY CONDUCT AND POLICIES

1. Research and publication ethics

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2. Disclosure of conflicts of interest

Financial sponsorship should be stated in the conflicts of interest. Any other financial support associated with the study, including stocks or consultation arrangements with pharmaceutical companies should be stated at the end of the text, under a subheading "Conflicts of interest."

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Human study must conform to ethical standards, and be approved by the appropriate Institutional Review Board (IRB). A statement concerning IRB approval and consent procedures must appear at the beginning of the "Methods" section. Any systematic data gathering effort in patients or volunteers must be approved by an IRB or adhere to appropriate local/national regulations. Authors may be questioned about the details of consent forms or the consent process. On occasion, the Editor-in-Chief may request a copy of the approved IRB application from the author.

4. Statement of human and animal right

Clinical research studies must state that the work was done in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki in 1975 (revised in 2013; http:// www.wma.net/en/30publications/10policies/b3/index. html). Clinical studies that do not meet the Declaration of Helsinki will not be considered for publication. Human subjects must not be identifiable. Patients' name, initial, hospital number, date of birth, or other protected health- care information must not be disclosed.

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The JIG follows the recommendations for authorship by the ICMJE, 2019 (http://www.icmje.org/icmje-recommendations.pdf) and Good Publication Practice Guidelines for Medical Journals 3rd Edition (KAMJE, 2019, https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13&per_page=). Authorship credit must be based on 1) substantial contributions to the concept and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors must meet the above four conditions.

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Main text

1) ***The main text should be structured as Introduction, Methods, Results, and Discussion.*** Use headings and subheadings in the Methods section and Results section. Every reference, figure, and table must be cited numerically in the order mentioned in the text.
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Chapter in a book: authors' name(s), title, number of editions, place of publication, publisher, year of publication, chapter number and title, and page numbers.

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Conference proceedings: author(s), paper title, In: editor(s), conference title, the year, place, place of publication, pub- lisher, year of publication, and page numbers.

Tables

1) Tables should be double-spaced and inserted on a separate page at the end of the text document, with the table number, table title and legend given above the table.
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Figures and figure legends

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Nonessential tables and figures may accompany articles as

online-only supplemental files. All online-only supplementary files should be combined in one document file (whenever possible) and uploaded separately during the submission process. This file must be clearly labeled as "Online-Only Supplemental Material." In addition, supplemental onlineonly files must be referenced in the main text of the manuscript at least once (e.g., "Supplemental Table S1").

All online-only supplemental files are subject to review, but such files will not be copyedited or proofread by EnM production staff. As such, authors are encouraged to review their supplemental files carefully before submitting them.

Lists that include names of principal investigators or writing groups may also be submitted as online-only supplements if they exceed 150 words. Otherwise, the names of principal investigators or writing groups should be listed in an appendix at the end of the main document, before the references.

3. Review article

A review article is a review focusing on a specific title and commissioned by the Publication Committee for publishing. Manuscripts submitted as review articles will be subjected to the same review process as original research articles. Instructions for original articles should be followed for review articles. A review article should include an abstract not exceeding 200 words, for which the number of references should not exceed 60.

4. Editorial

Editorials are commissioned for the purpose of commenting on a specific paper published by the journal, not to reflect the views of the Society. There is no limitation on the format. But an editorial should be written in no more than four pages (A4) with the number of references limited to 20.

5. Brief report

Short communications of original research are published as case report. The purpose of the category is to permit publication of very important, high-quality mechanistic studies that can be concisely presented. These manuscripts should include a short nonstructured abstract (150 words maximum), Introduction, Methods, Results, and Discussion.

The total manuscript length should not exceed 1,200 words, excluding references and abstract. Brief reports can include a maximum of 20 references and two figures or tables.

6. Image

Images that may help make clinical decisions while being interesting and educational in terms of the treatment of endocrinology and metabolism should be prepared with a manuscript. The manuscript should not be more than one page (A4), with the number of references limited to five.

7. Letters to the editor

A letter should contain constructive criticisms or comments on a specific paper published by the journal within the previous 6 months. The manuscript should be no more than one page (A4), with the number of references limited to five

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Correspondence Regarding Manuscript
Kyung Ran Jun, M.D, Ph.D.
Department of Laboratory Medicine, University of Inje,
875 Haeun-daero, Haeundae-gu, Busan 48108, Korea
E-mail: jun@paik.ac.kr