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Current Therapeutic Approaches for Hutchinson-Gilford Progeria Syndrome

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Hutchinson-Gilford Progeria Syndrome (HGPS; OMIM #176670) is a rare genetic disorder characterized by accelerated aging beginning in infancy. It is primarily caused by a *de novo* point mutation in the *LMNA* gene (c.1824C>T; p.G608G), which results in the production of progerin that disrupts nuclear integrity and promotes cellular senescence. The identification of LMNA gene has led to significant advances in targeted therapeutic research in the past 20 years. In this review, we will outline the pathophysiology of HGPS, and discuss the mechanism based therapeutic strategies, including recently approved drug, lonafarnib. We also address the multidisciplinary approach in the comprehensive management of patients with progeria.

Key words: Progeria, Therapeutics, Progerin, Lamin A, Rare disease

REVIEW ARTICLE

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INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS; OMIM #176670), also known as Progeria, is an ultra-rare genetic disorder characterized by fatal, rapidly progressive aging. The estimated prevalence is 1 in 20 million. Classic HGPS is caused by a *de novo* mutation in the *LMNA* gene (c.1824C>T; p.G608G), which leads to production of mutant lamin A, progerin. Affected infants appear normal at birth, but clinical features such as skin changes, growth failure, distinctive facial features and joint contracture, begin shortly after birth and progress over time. Average life expectancy is 14 years, primarily due to myocardial infarction and stroke resulting from rapidly progressing atherosclerosis [1-3]. Although HGPS was first described in 1886, management remained limited to symptomatic care until the early 2000s. The identification of the *LMNA* mutation and understanding of progerin's role have opened new avenues for targeted therapeutic research [4]. In this article, we review current and emerging treatment strategies, with a focus on their mechanisms of action and therapeutic potential.

PATHOPHYSIOLOGY OF HGPS: GENETIC MECHANISM, PROGERIN PRODUCTION, MOLECULAR MECHANISMS, RESEARCH MODEL

Classic HGPS is an autosomal dominant disorder mainly caused by *de novo* mutation in exon 11 of *LMNA* gene (c.1824C>T; p.G608G) located on chromosome 1q22 (Fig. 1A) [4]. The *LMNA* gene consists of 12 exons and encodes lamin A and lamin C, which are key structural components of the nuclear lamina [5]. Lamin A is initially synthesis as prelamin A and undergoes a series of post-transla-

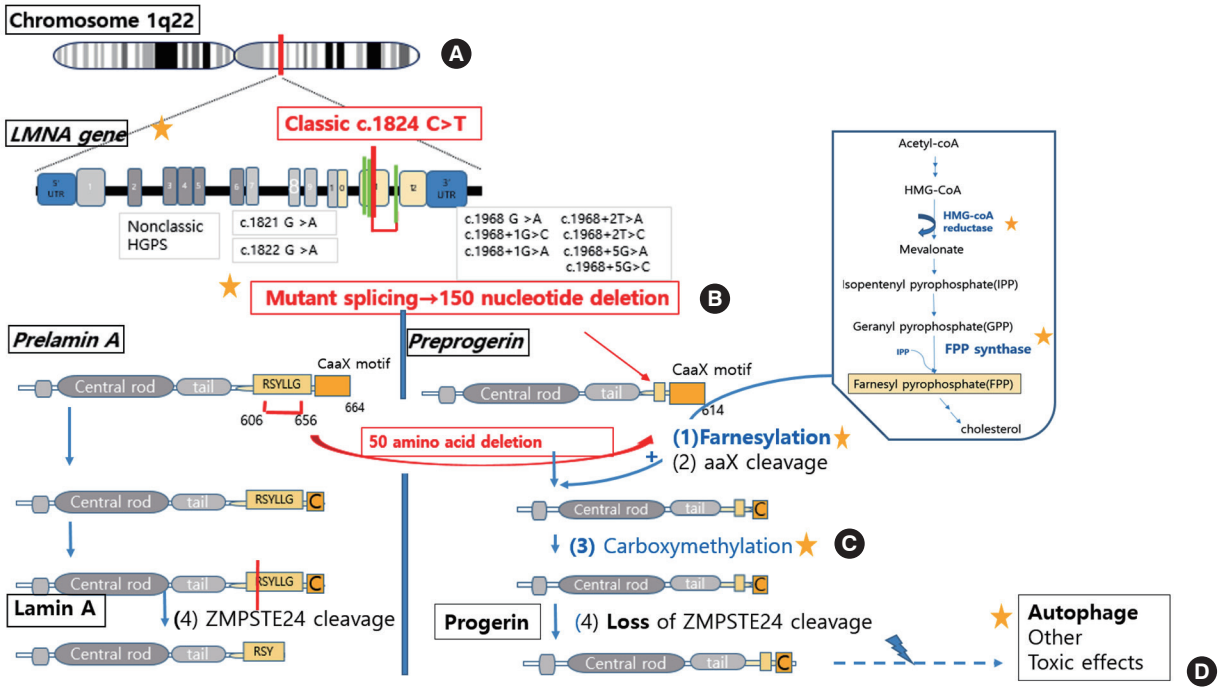


Fig. 1. Schematic illustration of the genetic and molecular mechanisms of progerin production in Hutchinson-Gilford Progeria Syndrome (HGPS). (A) *LMNA* gene is located on chromosome 1q22. (B) Classic HGPS is caused by a *de novo* c.1824C>T (p.G608G) mutation in exon 11, while non-classic HGPS is associated with other mutations in exon or intron 11. These mutations induce aberrant splicing, leading to a ~150 nucleotide deletion. (C) The deletion results in a truncated form of prelamin A, termed preprogerin, lacking 50 amino acids near the C-terminal region, including the ZMPSTE24 cleavage site. (D) Normally, prelamin A undergoes four sequential post-translational modifications: (1) Farnesylation of the C-terminal cysteine residue, (2) aaX cleavage by ZMPSTE24, (3) Carboxymethylation, and (4) final cleavage by ZMPSTE24 to generate mature lamin A. In HGPS, this final cleavage step is absent due to the loss of the cleavage site, resulting in the accumulation of permanently farnesylated progerin. Progerin accumulation leads to impaired autophagy and other toxic effects. Stars (*) indicate therapeutic targets designed to inhibit specific steps in the pathological process.

tional modifications to become mature lamin A (Fig. 1C):

1) Farnesylation: A farnesyl group is added to the cysteine residue within the C-terminal CaaX motif by farnesyltransferase.
2) -aaX Cleavage: The terminal three amino acids (-aaX) are cleaved off by the endoprotease ZMPSTE24.
3) Carboxymethylation: The exposed farnesylated cysteine residue is methylated by isoprenylcystein carboxylmethyltransferase (ICMT).
4) Cleavage of the farnesylated Tail: ZMPSTE24 removes the remaining 15 amino acids, including the farnesylated cysteine, producing mature lamin A. These modifications are crucial for the proper function and localization of lamin A within the nuclear lamina.

In classic HGPS, a mutation in exon 11 (c.1824C>T) induces aberrant splicing, results in the deletion of 50 amino acids nearby C-terminal region of prelamin A, producing a truncated protein known as preprogerin. Since the deleted region includes ZMPSTE24 cleavage site, final cleavage does not occur, leading to the accumulation of permanently farnesylated protein, progerin (Fig. 1D). Non-classic HGPS is associated with other *LMNA* pathogenic variants in exon 11 or intron 11 that results in production of progerin (Fig. 1B). Progerin accumulation disrupts nuclear organization and leads to epigenetic alterations, accelerated telomere shortening, mitochondrial dysfunction, defects in DNA damage response, altered p53 activation and autophagic degradation. These changes contribute to cellular aging and premature senescence. HGPS serve as a compelling model for studying genetic disorders, cellular senescence, clinical research, and regenerative medicine.

Progeria research models enhance understanding of its pathophysiology and developing of targeted therapies. Cellular models include HGPS patient-derived fibroblasts, iPSC-derived cells, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9-engineered gene edited models expressing progerin normal cells. Recently, organoid blood vessel

Table 1. Comprehensive overview of progeria therapeutic strategies

Therapy target		Drug	Mechanism
Genome editing		CRISPR-Cas9, ABE	Gene correction
Aberrant RNA splicing		ASO	Block aberrant splicing
Posttranslational modification	Mevalonate pathway	Statin, Bisphosphonate	Reduce progerin prenylation
: progerin production	Farnesylation	Lonafarnib (Zokinvy)	1st FDA approval drug
			Farnesyltransferase inhibitor
	Carboxymethylation	ICMT inhibitor	Block final maturation of progerin
Progerin clearance	Autophage activation	Everolimus, Rapamycin, temsirolims	mToR inhibitor
		Sulforaphane	Antioxidant
		Metformin, MG132	AMPK activation
	Mitochondrial dysfunction	Methylen blue	Antioxidant
Hazardous effects of progerin	Nuclear abnormalities	Progerinin (JH4 analogue)	Inhibit laminA /progerin binding
		Resveratrol, Leptomycin B, selinexor	CRM1 inhibitor- restore chromatin structure
			Normalize nuclear export
		Doxycycline	Alleviates the abnormal nuclear envelope
	DNA damage response	ATM inhibitor (KU-60019), methylene blue	DNA repair enhancement
		TERT circRNA(26)	Telomerase elongation
	Inflammation	Baricitinib, Vitexin	JAK-STAT inhibitor
		Dapansutrile (NLRP inhibitor),	Suppresses proinflammatory cytokines
		Tocilizumab (IL-6R inhibitor)	
	Endothelial dysfunction	Angiopoietin-2	Increase vascular health
		Vertepofin (YAP/TAZ inhibitor)	
	Stem cell depletion	Stem cell therapy	Replace damaged stem cells
	Senolytic	Dasatinib, Quercetin	Remove senescent cells

The therapies are categorized based on their mechanism of action, including genome editing, progerin production, progerin clearance, and reducing hazardous effecs of progerin. Bold text with line indicated that clinical trial has been conducted.
CRISRP/Cas, clustered regularly interspaced short palindromic repeats/CRISPR- associated protein 9; ABE, adenine base editing; ASO, antisense oligonucleotides; ICMT, isoprenylcystein carboxyl methyltransferase; ATM, ataxia-telangiectasia mutated.

models have also been utilized. *In vivo* models, *Lmna*$^{G609G/G609G}$ (HGPS Mouse Model) and *Zmpste24*$^{-/-}$ mice, which mimic laminopathy-related premature aging, tissue specific progerin producing model (progerin^{ecTg}, progerin^{VSMCTg}, etc.) as well as ApoE$^{-/-}$ mice further facilitate investigations into disease mechanism and therapeutic strategies (Table 1).

CURRENT THERAPEUTIC APPROACHES OF HGPS

Following the identification of *LMNA* mutations in 2003, therapeutic strategies for HGPS have progressed through several phases:

2003-2010: Drug repurposing

During this period, researchers focused on repurposing existing drugs to target progerin production and accumulation. Notably, farnesyltransferase inhibitor (FTIs), initially developed for cancer treatment, were employed to inhibit the farnesylation of progerin, aiming to reduce its deleterious effects.

2010-2020: Combination therapies and enhancement of cellular clearance mechanisms.

The therapeutic approach evolved to include combination therapies that not only targeted progerin modification but also enhanced its clearance. For instance, combining FTIs with statins and aminobisphosphonates aimed to prevent alternative prenylation pathways. Additionally, agents like rapamycin were investigated for their potential to promote autophagic degradation of progerin.

2020-Present: Gene-based and regenerative approaches, aiming for disease reversal.

Recent advancements have shifted towards gene-based therapies, including CRISPR/Cas9-mediated correction of the LMNA mutation, offering the potential for disease reversal. These approaches aim to directly address the underlying genetic defect responsible for HGPS.

These evolving strategies reflect a comprehensive effort to mitigate the effects of HGPS, ranging from modifying post-translational processing of progerin to correcting the genetic mutations at their source.

1. FTI (Fig. 1C-(1), farnesylation*)

FTIs were originally developed as anticancer agents. These compounds to bind to the farnesyltransferase CAAX motif on progerin, preventing its farnesylation and subsequent progerin accumulation. By inhibiting this post-translational modification, FTIs mitigate the toxic effects of progerin in HGPS.

Lonafarnib (Zokinvy) is the first FDA approval drug for HGPS and progeroid laminopathy at 2020 [6]. A phase 2 clinical trial (NCT 00425607) enrolled 25 patients over 2 years to access efficacy compared to an untreated HGPS cohort. The study demonstrated that Lonafarnib extended mean survival by 2.5 years over an 11-year follow-up period. Additional benefits observed in treated patient included improvements in weight gain, bone density, arterial functions, and hearing. However, gastrointestinal side effects such as nausea and diarrhea were reported in up to 80% of patients [7]. Lonafarnib is administered orally and is approved for patients ≥ 12 months old with body surface area (BSA) of ≥ 0.39 m^2.

2. Statin and Bisphosphonate* (Fig. 1, ▯ box)

Statin, and bisphosphonate inhibit progerin prenylation, by reducing production of protein required for farnesylation. Preclinical studies demonstrate improved bone and vascular function, however clinical trials showed no superiority compared to lonafarnib monotherapy. These treatments can be considered selectively for patients with severe osteoporosis or high cholesterol, but potential for side effects like myopathy and bone pain.

3. ICMT* inhibitor (Fig. 1C-(3))

ICMT inhibitors target the carboxymethylation step, post-translational modification of progerin. *In vitro* studies have shown that ICMT inhibitors delocalized progerin from the nuclear membrane, reduced DNA damage, and increased cellular viability. *In vivo* mouse model, it extended lifespan, improved grip strength, and reduced tissue senescence without notable toxicity [8]. Further studies are warranted to validate its safety and efficacy.

4. mTOR inhibitor and other drugs enhance autophagy* to progerin removal

mTOR inhibitor enhance autophagy-mediated progerin clearance, reducing nuclear abnormalities, senescence, and DNA damage levels in HGPS fibroblasts [9-11]. Among them, Everolimus, rapamycin, temsirolimus have been investigated for progeria. Everolimus is preferred due to its superior tissue penetration, ease of control owing to its short half-life, and relatively mild side effect profile [12,13]. Common side effects of mTOR inhibitors include an increased risk of infection due to immunosuppression, peripheral edema, dyslipidemia, hyperglycemia and delayed wound healing. A Phase I/II clinical trial on everolimus and lonafarnib combination therapy for HGPS has been conducted to evaluate everolimus and lonafarnib combination therapy in HGP.

Sulforaphane is an antioxidant derived from cruciferous vegetable and stimulates proteasome activity and autophagy studied in *in vivo* therapy. Methylene blue improves mitochondrial dysfunction and increases autophagy *in vitro*. MG132 is a proteasome inhibitor, induce macroautophagy and, also act on reducing progerin production through splicing regulation by downregulate splicing factors. Metformin induces activation of AMP-activated protein kinase (AMPK) and mTOR inhibition.

5. Antisense oligonucleotide (ASO) therapy

ASO therapy corrects the LMNA splicing error and reduces progerin production at the mRNA level. The study in mice shows a 50-60% increase in lifespan and human trials are forthcoming [14]. However, ASO therapy faces limitations, including a lack of improvement in cardiovascular pathology, the need for repeated administration, and the possibility of off-target effects.

6. Gene editing (CRISPR and base editing)

CRISPR/Cas 9 and adenine base editing (ABE) correct the *LMNA* mutation at DNA level and offers a potential one-time cure. In progeria mouse models, base editing doubled lifespan, demonstrating curative potential [15,16]. It is still experimental in humans. It may induce immunogenicity and requires safe and effective delivery methods. Off-target genetic modifications remain a concern.

7. Therapies for other toxic effects of progerin

JH4 is a small molecule—a low-molecular-weight compound capable of modulating intracellular interactions—that acts as a progerin and lamin A binding inhibitor. Progerinin is an orally administered analog of JH4, developed to improve the pharmacokinetic and therapeutic properties. It reduces progerin levels and prevents progerin from damaging the nuclear lamina. In a study in mice, progerinin improved aging phenotype and cardiac dysfunction. It also extended the lifespan by approximately 50%, demonstrating better results than

lonafarnib [17,18]. A clinical trial for combination therapy with lonafarnib is planned (NCT06775041). Other drugs that target nuclear abnormalities include Chromosomal Region Maintenance 1 CRM1 (CRM1) inhibitor such as leptomycin, resveratrol, selinexor [19], and doxycycline [20]. CRM1 inhibitor normalize the nucleocytoplasmic partitioning of proteins, modulate chromatin accessibility, and decrease progerin levels. Additionally, doxycycline has been explored for its potential role in nuclear homeostasis.

Progerin accumulation exacerbates inflammation in progeria. JAK-STAT inhibitor (Baricitinib, Vitexin) [21], NLRP inhibitors (dapansutrile) [22], anti-IL6R inhibitory Antibodies (Tocilizumab) [23] have been studied. These drugs modulate proinflammatory cytokines and impact on senescence *in vitro* and *in vivo* models. Progerin accumulation also disrupts normal DNA repair mechanisms, accelerated telomere shortening, and increases genomic instability. Therapies targeting DNA damage repair include ATM inhibitors (e.g., KU-600196) [24], methylene blue [25], and TERT circRNA [26].

Endothelial dysfunction is the main pathogenesis of progeria-associated atherosclerosis. Therapeutic approaches targeting this mechanism include Verteporfin (YAP/TAZ inhibitor) *in vitro* study [27], and angiopoietin-2 in mouse models [28]. From a regenerative medicine perspective, progeria is characterized by premature stem cell exhaustion and chronic inflammation. Consequently, stem cell-based therapies are under investigation and have demonstrated improvements in body composition, arterial elasticity, and systemic inflammatory markers in patients [29,30]. Senolytic therapies such as Dasatinib, Quercetin are also explored as potential treatment for cellular senescence.

8. Combination therapies with lonafarnib

1) Zoledronate+Pravastatin (ZOPRA)+Lonafarnib (NCT00916747)

A clinical trial involving 37 patients evaluated the combination therapy with statins and bisphosphonates targeting the mevalonate pathway to prevent farnesylation. The study found that, aside from an increase in bone mineral density, this combination therapy did not demonstrate superior efficacy compared to monotherapy [31]. Additionally, an increased amount of abnormal donut-shaped nuclei was observed in patients receiving the combination therapy [32].

2) Everolimus+Lonafarnib (NCT02579044)

Improved endothelial function and vascular stiffness *in vitro* 3D blood vessel model [13] and currently combination clinical trial is ongoing state.

3) Progerinin+Lonafarnib (NCT06775041)

A phase 2 clinical trial of combination therapy is recruiting now. Progerinin is a JH4 analog that inhibits the binding of progerin to lamin A. In the *in vivo* model, progerinin was more effective than lonafarnib alone or in combination [18].

4) Other research with Lonafarnib in vitro and in vivo

Additional combination therapies with barcitinib, dapansutrile, and sulforaphane has been studied to improve efficacy. Baricitinib (JAK-STAT inhibitor) reduce toxicity of FTI, and improve nuclear morphology, restoring proteostasis and alleviating inflammation and senescence in HGPS fibroblasts [33]. Dapansutrile (NLRP3 inhibitor) with lonafarnib reduced progerin accumulation, inflammation, and senescence, leading to extended survival and improved phenotypes compared to lonafarnib alone in animal model [22]. Sulforaphane is antioxidant and increases autophagy. Not concomitant, cross repeated administration with lonafarnib improves cellular homeostasis [34].

9. Multidisciplinary clinical approach

Multidisciplinary care is central to improving the quality of life for patients with HGPS. Cardiac care includes regular monitoring of blood pressure, lipid profile, EKG and echocardiography performed at least annually. If possible, pulse wave velocity and carotid intima media thickness should also be considered. An immediate brain MRI with angiography is required when symptoms like headache, seizures or muscle weakness occur. To prevent stroke, low dose aspirin and adequate hydration (1-1.5 L/day) are recommended. Annual ophthalmologic and audiologic exams are also essential. Supportive strategies including a high-caloric diet, rehabilitation therapy, and use of shoe inserts can help maintain daily function [35].

CONCLUSION

Over the past two decades, our understanding of HGPS has deepened with uncovering LMNA gene mutation and elucidation of progerin production and its pathologic effects. This progression led to active research by repurposing drug targeted mechanisms. One major breakthrough came with the FDA approval of lonafarnib, a farnesyltransferase inhibitor, which prolongs the lives of patients with HGPS. However, it has lim-

ited efficacy in some aspects, such as dermatologic and joint contractures, and does not halt disease progression. Because of these shortcomings, the research trends have shifted toward combination therapies that target multiple mechanisms. Also, many innovative treatments, such as genetic, regenerative approaches, are currently under investigation. Genome-editing technologies, such as CRISPR-Cas9 and ABE, present promising avenue as potential one-time curative options. Clinical trials of stem cell therapies in HGPS patients are also ongoing. Still, further research is required to evaluate the long-term safety and efficacy, and to carefully assess the limitations of real-world clinical use. Our goal for HGPS treatment should be to refine combination treatment and translate preclinical advances into clinical practice. Additionally, comprehensive management with a multidisciplinary approach will improve treatment outcomes. Continued commitment to this work could lead to safer, more effective ways to manage HGPS in the future.

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Feasibility of Artificial Intelligence-Based Severity Assessment Technique Using Stimulated Muscle Contraction Signal in the Patients with Spinal Muscular Atrophy

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Background: The Hammersmith Functional Motor Scale-Expanded (HFMSE) is a clinical instrument used to evaluate motor function in the patients with spinal muscular atrophy (SMA). Conventional approaches, such as the manual muscle test (MMT), are often used to assess muscle strength. We propose a severity assessment technique for patients with SMA using the stimulated muscle contraction signal (SMCS), a quantitative technique to evaluate the severity of the disease by synthesizing functional motor assessment and muscle strength. The objective of the present study is to demonstrate the feasibility of the severity assessment technique using electrical stimulation signals.
Methods: A severity assessment index has been defined, including both functional motor assessment score and muscle strength. The methodology employed entails the acquisition of bio-signals related to the condition of the neuromuscular system, followed by a feature extraction procedure. The bio-signals are processed through this procedure, yielding an extracted feature vector that is subsequently fed into an artificial intelligence (AI) model. This ultimately results in the assessment of severity. In addition, since the index for severity encompasses both the functional motor assessment score and muscle strength, we also verified whether the AI model could estimate each index.
Results: The performance of the proposed technique was validated using a database consisting of 21 patients with SMA. The comparison between the model's estimated values and the labeled values based on a Pearson correlation showed a coefficient of 0.76.
Conclusion: The proposed technique was able to estimate the two indices, thereby demonstrating its capability to effectively estimate the defined severity index.

Key words: Spinal muscular atrophy, Artificial intelligence, Functional motor assessment, Manual muscle test, Stimulated muscle contraction signal

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INTRODUCTION

Spinal muscular atrophy (SMA) is a monogenic neurodegenerative disease that is autosomal recessively inherited. Its incidence is estimated to be approximately 1:6,000 to 1:10,000 in newborns [1]. SMA is the most prevalent motor neuron disease (MND) in children. Motor neuron diseases impede the transmission of electrical signals from motor neurons located within the spinal cord to motor nerves, consequently inducing accelerated motor nerve degeneration [2-5]. In clinical practice, physicians utilize functional motor assessments, such as the Hammersmith Functional Motor Scale-Expanded (HFMSE), to evaluate the severity of function and performance status in patients with SMA [6,7]. Additionally, the manual muscle test (MMT) is employed to assess muscle strength [8]. However, these methods entail subjective evaluation, which hinders the attainment of objective severity assessments [9,10].

Most patients diagnosed with SMA encounter challenges related to their mobility due to motor weakness. Consequently, these patients often face difficulties in maintaining frequent hospital visits for clinical evaluations and functional assessments. To overcome the limitations of mobility and subjective assessment meth-

ods, a technology has been proposed that uses wearable devices and artificial intelligence (AI) to assess the severity of neurological disorders [11,12]. The impact of neurological disorders on the neuromuscular system emphasizes the need for the collection of physiological information. A key pathological feature of neuromuscular disease is the reduction in the cross-sectional area (CSA) of both myelin, which envelops motor neurons, and muscle fibers, ultimately leading to a decline in motor function [13-15]. Given the critical role of motor neurons and muscle fibers in movement, obtaining detailed information about these structures is essential for evaluating the severity of disease. The first step is to collect response signals that are triggered by electrical stimulation of the neuromuscular system. When a muscle is stimulated, the motor nerve and muscle fibers are activated, and surface electromyography (sEMG) records response signals from both the motor nerve and muscle fibers [16-20]. The previous studies have used compound muscle action potential (CMAP) signals to study muscle function evaluation [21-23]. To assess the severity of neuromuscular disease (NMD) based on the pattern of muscle response signals, long-term electromyography was recorded using electrical stimulation of various frequencies. These signals were defined as stimulated muscle contraction signals (SMCS) [24].

We propose an AI technique that estimates the defined index using SMCS, which includes bioinformation about the neuromuscular system. The aim of this study is to determine whether the SMCS can effectively reflect functional motor performance and muscle strength.

MATERIALS AND METHODS

1. Participants

This study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent prior to enrollment. The study protocol was approved by the institutional review board (IRB No. 04-2022-034) of Pusan National University Yangsan Hospital. This cross-sectional study was conducted from March 2023 to December 2024. The inclusion criteria encompassed a genetic diagnosis of SMA. Exclusion criteria encompassed patients with (a) intellectual disabilities; and (b) neurological deficits other than SMA.

2. Severity assessment index

The Hammersmith Functional Motor Scale Expanded is a clinical assessment tool designed to evaluate motor function in individuals with SMA types 2 and 3, particularly those with higher functional abilities [25]. The final severity score is determined by aggregating the individual item scores. To complement the functional motor assessment, measurement of the maximum muscle strength of subjects at the ankle, knee, wrist, and elbow is necessary. The objective muscle strength was measured using a dedicated muscle strength assessment device (microFET2, HOGGAN, USA).

As disease progresses, different muscle groups experience varying degrees of weakness depending on the individual patient. This underscores the necessity for a multifaceted evaluation approach, incorporating diverse metrics to comprehensively assess SMA severity. To address this limitation, we performed an integrated approach that combines functional motor assessment scores with muscle strength values. Specifically, we defined the severity of NMD denoted as f, by constructing a feature vector that incorporates both functional assessment scores and strength measurements from multiple joints.

The formulation is as follows:

$$f=(w^2+h_{UL,NOR}^2)^{1/2}+(x^2+h_{LL,NOR}^2)^{1/2}+(y^2+h_{UL,NOR}^2)^{1/2}+(z^2+h_{LL,NOR}^2)^{1/2} \quad (1)$$

$$h_{UL,NOR}=h_{UL}/h_{UL,MAX} \quad (2)$$

$$h_{LL,NOR}=h_{LL}/h_{LL,MAX} \quad (3)$$

Where w, x, y, and z are muscle strength at ankle, muscle strength at knee, muscle strength at wrist, and muscle strength at elbow respectively. And h_{UL} and h_{LL} are results of functional motor assessment for upper limb and lower limb. At this time, since h_{UL} and h_{LL} have different maximum scores, the final outcome might be influenced by the scale difference. Therefore, we normalized using the maximum scores, as in equations (2) and (3), to obtain $h_{UL,MAX}$ and $h_{LL,MAX}$. As w and x represent muscle strength for the lower limb, we defined $h_{LL,MAX}$ and lower limb muscle strength as a single vector. Similarly, since y and z represent muscle strength for upper limb, we defined $h_{UL,MAX}$ and upper limb muscle strength as a single vector.

Additionally, considering the inherent differences in muscle strength distribution between the upper and lower limbs, we performed standard deviation-based normalization within the collected database. Specifically, each muscle strength value was adjusted based on its deviation from the maximum, ensuring that differences in scale do not distort the severity evaluation. By applying these normalization techniques, we addressed the imbalance between functional motor assessment scores and muscle strength measurements, ensuring that the metric contribute equally to the severity evaluation. Finally, we defined a

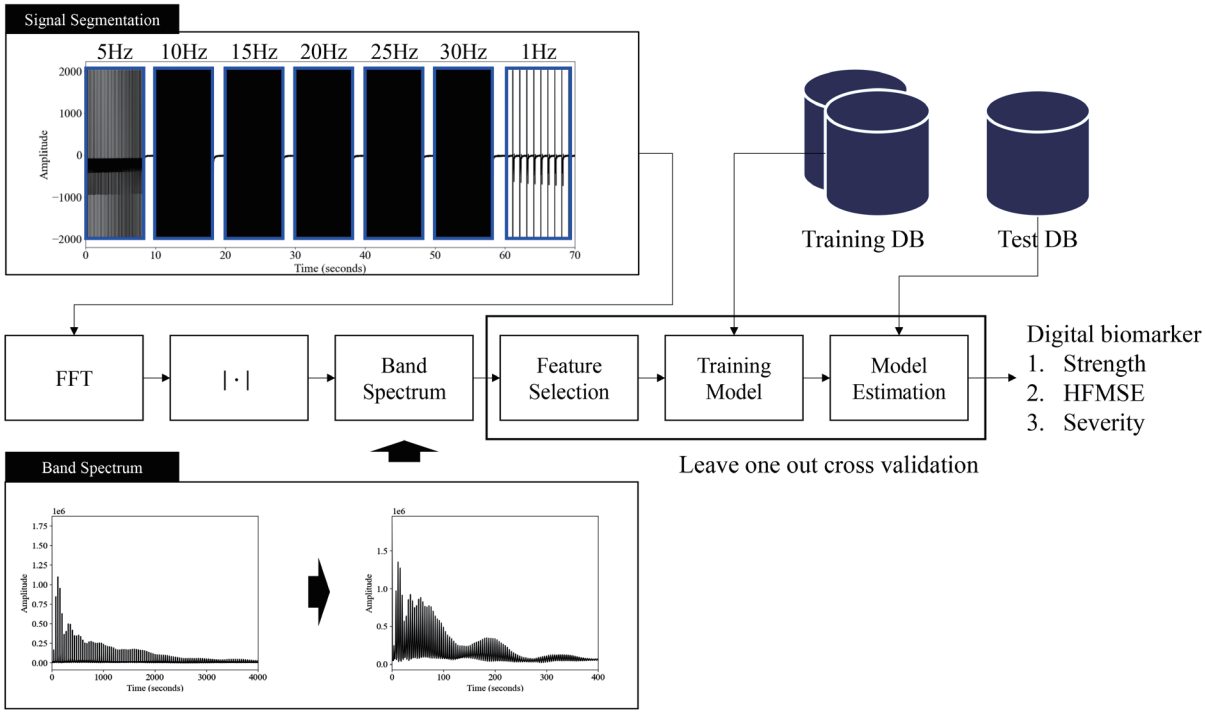


Fig. 1. Total block diagram.

severity assessment index that integrates muscle strength across multiple joints and functional motor assessment results to provide a comprehensive measure of SMA severity.

3. Technical method

The proposed system is structured as illustrated in Fig. 1. The process commences with the collection of SMCS using a wearable device equipped with sEMG sensors. This device was designed to record muscle response signals while concurrently delivering electrical stimulation to the target muscles. The stimulation was initiated at an initial frequency of 5 Hz, with data being recorded for a period of 8 seconds. Thereafter, the stimulation frequency was progressively augmented in 5 Hz increments, reaching up to 30 Hz.

The collected SMCS data was then segmented according to the applied stimulation frequencies. From these segmented signals, feature vectors were extracted using frequency-specific feature extraction techniques. Spectrum analysis through the Fast Fourier Transform (FFT) was employed to derive meaningful features from the SMCS, which serve as inputs for an AI model. To effectively interpret the frequency characteristics of the data, an artificial neural network (ANN) was utilized for model training and analysis.

1) Bio-signal for neuromuscular system

As shown in Fig. 2, the wearable device (exoPill, EXOSYSTEMS Inc., Korea) is an integrated electrostimulator and sEMG sensor with four exposed electrodes on the underside. These electrodes interface with hydrogel pads and magnets, ensuring a secure connection between the device and skin on the target muscle. The following six body parts were used for the collection of SMCS with the exoPill attachment: the anterior arm (lower flexors), the anterior forearm (wrist flexors), the anterior thigh (knee extensors), the anterior lower leg (ankle extensors), the posterior thigh (knee flexors), and the posterior lower leg (ankle flexors). exoPill is wirelessly connected to a smartphone application, which provided guidance during the data acquisition process. The SMCS data, recorded in accordance with the application's instructions, was automatically transmitted and stored on a central server.

2) Segmentation and spectrum-based feature extraction

Since the signals were recorded under electrical stimulation at various frequencies from 5 Hz to 30 Hz, each segment exhibited unique frequency characteristics. Therefore, the segmented signals were analyzed individually to account for these fluctuations before feature extraction. Features with an absolute correlation coefficient greater than 0.25 were selected as

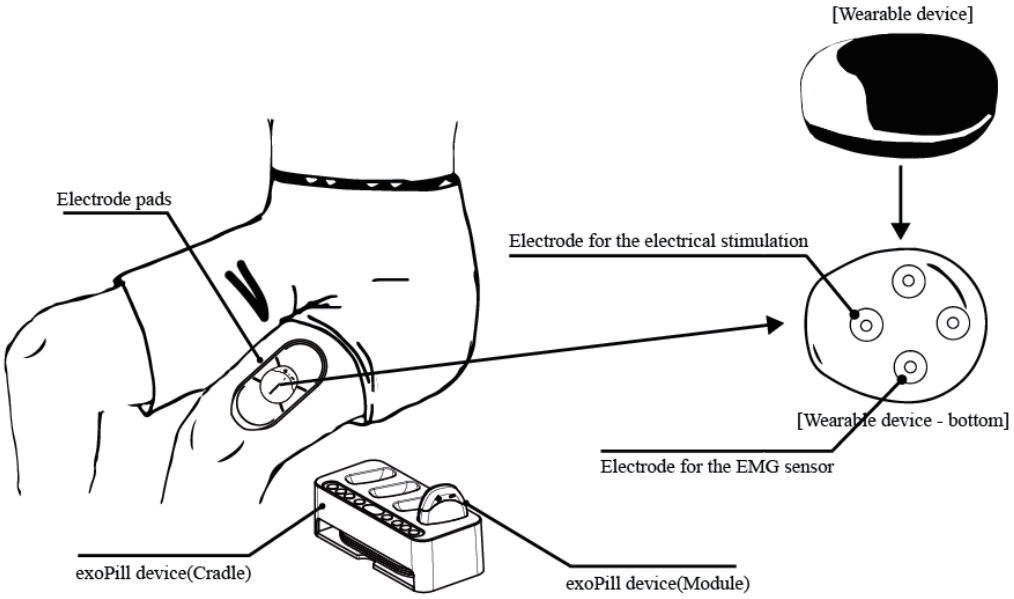


Fig. 2. Outline for structure description of wearable device (exoPill, EXOSYSTEMS Inc., Korea).

the AI input vector. Leave-One-Out Cross-Validation (LOOCV) was performed, and feature selection was performed on the training data set before model training to optimize the feature representation.

3) Model training

The training procedure for the ANN regression model consisted of two major stages. First, the model parameters were initialized to ensure a stable starting point for learning. This initialization was performed using a uniform distribution centered around zero [26]. Next, the model underwent fine-tuning through backpropagation, which iteratively updates the weight matrices and bias vectors to optimize performance [27]. During this process, we utilized the logistic activation function to enhance learning stability and employ mean squared error (MSE) as the loss function to measure estimation accuracy.

The ANN architecture consists of two hidden layers with (16, 16) units, respectively. To prevent overfitting, a L2 regularization was applied during training, ensuring model generalization. Finally, the ANN model was trained to estimate digital biomarkers for severity of SMA, leveraging the extracted feature vectors to provide meaningful insights.

RESULTS

1. Characteristics of subjects

A total of 21 patients with SMA participated in this study. Of these, 14 were diagnosed as type 2, while the remaining seven were diagnosed with type 3. The mean age was 26.1 with 14.4 standard deviation. The mean of height and body weight were 151.6 cm with 14.8 cm standard deviation and 42.8 kg with 17.4 kg standard deviation, respectively. And the mean of HFMSE score was 21.3 with 19.8 standard deviation.

2. Experimental results

In the scatter plots shown in Fig. 3A, B, and C, the *x*-axis represents the model estimations and the *y*-axis represents the actual value, and a significant correlation was observed between the estimate and the actual value. The ANN models trained to estimate the functional motor assessment index and muscle strength index individually exhibited reasonable predictive performance. The quantitative evaluation results for the trained model are summarized in Table 1. The correlation coefficient was 0.76, and the standard deviation of errors for the severity digital biomarker was 3.35.

In the Bland-Altman plots shown in Fig. 3D, E, and F, the observed errors appear to be distributed uniformly across the entire range, thereby suggesting a low degree of bias in the trained model. Therefore, the analysis of the Bland-Altman plot suggests that the proposed AI model was trained in a balanced manner without bias. Furthermore, the model designed to estimate the severity digital biomarker, which integrates both indices, also yielded highly significant results, supporting the validity of the proposed approach.

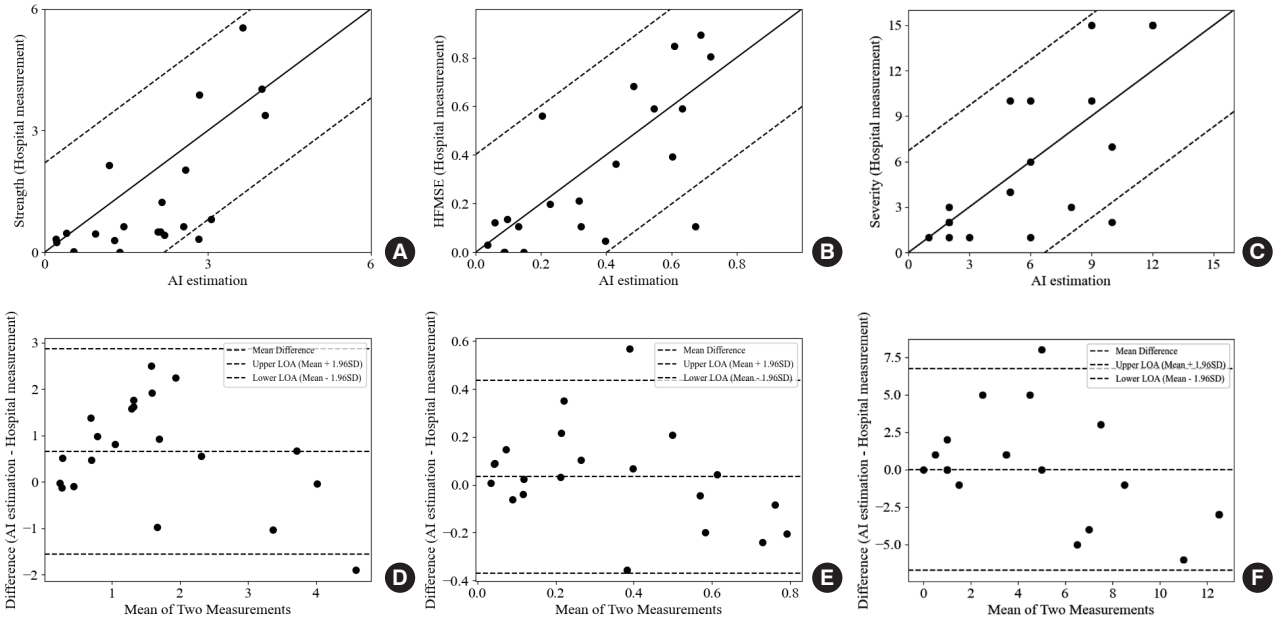


Fig. 3. Scatter plot for labels and model estimation. (A) Estimated result of the data from the functional motor assessment model. (B) Estimated result of the data from the muscle strength. (C) Estimated result of the data from the digital biomarker. (D) Estimated result of all data from the functional motor assessment model. (E) Estimated result of all data from the muscle strength model. (F) Estimated result of all data from the digital biomarker model.

Table 1. Model estimation for functional motor assessment, muscle strength, and digital biomarker

Functional motor index				Muscle strength				Digital biomarker for severity			
ME	STDE	*r*	*P*-value	ME	STDE	*r*	*P*-value	ME	STDE	*r*	*P*-value
0.03	0.20	0.74	<0.001	0.66	1.10	0.70	<0.001	0.00	3.35	0.76	<0.001

p-value for Pearson correlation coefficient. ME, mean error; STDE, standard deviation of error.

DISCUSSION

This study demonstrates the feasibility of an AI-based technology using SMCS to assess the severity of SMA. The severity index comprises two clinical measures: muscle strength and functional motor assessment score. Therefore, the efficacy of the proposed method in estimating the severity index should also represent the ability to estimate each individual component. To validate this hypothesis, we trained AI models to predict both muscle strength and functional motor assessment score using SMCS data as the input. The experimental results demonstrated statistically significant correlations between the model estimates and the clinical measurements, MMT and HFMSE. These findings suggest that SMCS contains relevant information related to muscle strength and functional motor performance, demonstrating the potential of the proposed method for quantitative assessment of neuromuscular function.

Several studies have investigated the correlation between features derived from CMAP signals collected from SMA patients and functional assessment. When the features extracted from the CMAP signals were compared with muscle strength and HFMSE, a strong correlation ranging from 0.73 to 0.79 was found [28,29]. These findings imply a close relationship between the neuromuscular bio-signal CMAP and muscle motor function. Since SMCS signals are measured using a similar principle to CMAP, it is confirmed that SMCS can be used to assess muscle strength and functional score such as HFMSE.

Increasing the frequency of electrical stimulation in SMCS resulted in a decrease in the duration of the observable response signal between stimulation pulses. At 35 Hz, the response signal was barely distinguishable due to overlapping stimulation artifacts. Therefore, in this study, stimulation frequencies were limited to a maximum of 30 Hz. Although this study limited the electrical stimulation frequency to 30 Hz or below, it is possible that important information related to neuromuscular re-

sponses exists in higher-frequency stimulation above 30 Hz. Although a range of stimulation frequencies was explored in previous studies [30,31], the parameters used therein may not be fully optimized for the proposed system. To further enhance the performance and reliability of the proposed technique, future studies are needed to determine the optimal stimulation frequency.

There are several limitations in this study. First, SMCS in the proximal joints such as shoulder or pelvic girdle muscles were not included. Because proximal joints have a high degree of freedom and many involved muscles, it is difficult in measuring and analyzing signals in one direction with various muscles. Muscle strength of proximal joints plays a crucial role in performing functional movements in activities of daily livings. Therefore, future study should include proximal muscle strength to better represent the relationship between functional assessment and muscle strength. Second, the HFMSE was used in the assessment of motor function; however, it primarily reflects gross motor abilities and does not capture upper extremity fine motor function. Including an evaluation of upper extremity function, along with both gross and fine motor skills, would provide a more thorough representation of actual functional capabilities.

As of March 2025, SMA treatments have advanced significantly with the FDA-approved three disease-modifying treatments: antisense oligonucleotide nusinersen, gene replacement therapy onasemnogen abeparvovec, and small molecule splicing modifier risdiplam [32]. These treatments target the survival motor neuron protein deficiency, which results in an extended life span and improved quality of life for people with SMA. Given that these innovative treatments can have a lifelong impact, there is a need for a way to detect and manage the disease characteristics associated with the treatment. We expect that AI-based technologies that use SMCS to assess the severity of SMA will be further developed and become one of the options to objectively measure the functional status of individuals with SMA.

CONCLUSION

The present AI-based system, utilizing SMCS, has been developed for the purpose of evaluating the severity of SMA. SMA directly impacts the neuromuscular system. Consequently, it is imperative to obtain neuromuscular information for an accurate assessment of the severity of the disease. The SMCS data demonstrated a strong correlation between the AI model estimates and the clinical assessment data, indicating the model's potential for reliable disease severity assessment. The present AI-based system has the advantage of enabling severity assessment with improved accessibility and convenience. This is particularly advantageous for individuals with limited mobility due to SMA.

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JIG Journal of Interdisciplinary Genomics

Instruction for Authors

Revised 3rd: June 23, 2023

Enacted in January 31, 2019 and most recently revised in June 23, 2023 and applied from Vol 5, No 2 (October 2023)

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