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The Firsts in the Chronicle of Gene Therapy: Triumphs and Tragedies in Treating Inherited Disorders

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This review chronicles the pivotal "firsts" in gene therapy, from early successes like the 1990 *ex vivo* trial for adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID) to the profound setbacks that shaped its trajectory. Tragic events, including leukemia from insertional mutagenesis in SCID-X1 trials and the death of Jesse Gelsinger from a catastrophic immune response, forced a critical re-evaluation of vector safety and regulatory oversight.
This introspection led to the development of safer adeno-associated virus (AAV) vectors and the landmark success of *in vivo* therapy with Luxturna for Leber's congenital amaurosis. The path to commercial viability saw the failure of Glybera contrasted with the blockbuster success of Zolgensma for spinal muscular atrophy, paving the way for the current era of CRISPR-based gene editing with the approval of Casgevy. This history reveals a field matured through adversity, now delivering transformative therapies while still facing critical challenges in cost, immunogenicity, and long-term durability.

Key words: Gene therapy, Adverse events, Genetic disorders

REVIEW ARTICLE

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INTRODUCTION: FROM CONCEPT TO CLINIC

The idea of correcting defective genes has long been the ultimate ambition of genetic medicine. Ever since the discovery that genetic information resides in the threads of nucleic acid—and that minute errors within it can profoundly impact human health—the great minds of science have been irresistibly drawn to finding a way to patch these flaws.

However, the "find-and-fix" concept proved far more complex than early optimism suggested. The field lacked efficient vectors to deliver genes to target tissues and a deep understanding of the immune system, which is inherently resistant to any foreign genetic material. As technology advanced to overcome these biological hurdles, the regulatory paradigm also had to evolve to oversee unprecedented studies on human subjects.

EARLY DAYS OF GENETIC ENGINEERING

In the 1950s, the DNA double helix was first identified as the core genetic material. It was found to replicate itself, with its information transcribed into RNA and then translated into protein by elaborate cellular machinery. The following decades brought foundational discoveries in molecular biology, enabling scientists to isolate, multiply, analyze, and recombine DNA sequences. A landmark achievement occurred in 1978 when recombinant human insulin was produced using *E. coli* bacteria expressing the human insulin gene [1].

By the 1980s, genes responsible for Mendelian diseases began to be cloned,

starting with X-linked chronic granulomatous disease and Duchenne muscular dystrophy, followed by cystic fibrosis and Huntington's disease. Since many of these conditions were caused by a loss of gene function, delivering a functional copy of the missing gene seemed a straightforward and irresistible challenge for enthusiastic researchers.

FIRST SUCCESSFUL GENE THERAPY: SEVERE COMBINED IMMUNODEFICIENCY (ADA-SCID)

Adenosine deaminase (ADA) deficiency is a rare genetic disorder that devastates the immune system, falling under the umbrella of severe combined immunodeficiency (SCID). The ADA enzyme is responsible for breaking down deoxyadenosine, a substance toxic to lymphocytes. Patients with ADA-SCID are susceptible to recurrent, life-threatening infections, with treatment options limited to bone marrow transplantation and enzyme replacement therapy.

Ashanthi DeSilva, diagnosed with ADA-SCID at age two after recurrent infections. Enzyme replacement therapy with pegylated ADA incompletely recovered her immune system. A matching bone marrow donor could not be found. In 1990, at four years old, she was enrolled in a landmark gene therapy trial, which was meticulously prepared for several years [2]. The treatment was an *ex vivo* gene therapy: her T lymphocytes were obtained via apheresis, expanded in culture, and transduced with a retroviral vector carrying a functional *ADA* gene. These corrected cells were then reinfused into her bloodstream [3].

The therapy was a remarkable success. The engineered T-cells began producing the ADA enzyme, significantly improving Ashanthi's immune function. The T-cells outlived much longer than expected. Although she continued to receive supplemental enzyme replacement therapy, the gene therapy allowed her to lead a normal life, becoming a genetic counselor.

Despite this initial triumph, subsequent trials using similar or more advanced technologies failed to replicate the same degree of success. However, the pioneering work led to the 2016 EMA approval of Strimvelis, an autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with the retroviral vector that encodes for the human ADA cDNA sequence. It is the first *ex vivo* gene therapy approved for clinical use.

FIRST CANCER CAUSED BY GENE THERAPY: SCID-X1

Another type of SCID, popularized by the "bubble boy" of the 1970s, is caused by defects in the *IL2RG* gene on the X chromosome and is known as SCID-X1. Researchers in Paris (1999) and London (2001) devised similar *ex vivo* gene therapy trials, but with a key difference: they transduced hematopoietic stem cells from bone marrow with a retrovirus carrying the *IL2RG* gene.

The immunologic outcomes were initially successful, with treated infants recovering functional immune systems [4] that lasted for over a decade [5]. Tragically, this success was overshadowed when six of the 19 subjects developed T-cell acute lymphoblastic leukemia 2-14 years after treatment, which was fatal in one case. The cause was insertional mutagenesis: the retroviral vector integrated into the host genome near a proto-oncogene, *LMO2* for example, activating it and leading to the uncontrolled growth of T-cells. This devastating adverse event halted many gene therapy trials and spurred the development of safer vectors, such as self-inactivating retroviruses and lentiviruses [6].

FIRST DEATH CAUSED BY GENE THERAPY: THE CASE OF JESSE GELSINGER

Ornithine transcarbamylase (OTC) deficiency is an X-linked disorder of the urea cycle, which metabolizes toxic ammonia into urea for excretion. The resulting hyperammonemia is devastating to the brain, and neonatal-onset cases have a grim prognosis.

Jesse Gelsinger was an 18-year-old with a milder, late-onset form of OTC deficiency. He lived a relatively normal life managed with a low-protein diet and numerous medications, though he had experienced several metabolic crises that required interventions. In 1999, he enrolled in a Phase 1 clinical trial at the University of Pennsylvania, which used an adenovirus vector to deliver the *OTC* gene. Seventeen other subjects had been treated before him.

The day before his injection, Jesse's ammonia levels were elevated, but this was overlooked as it was not an explicit exclusion criterion. The day after the infusion, he developed jaundice and rapidly deteriorated into a coma, to expire in four days.

It was only after his death that his family learned of critical undisclosed information: monkeys had developed severe liver

damage in preclinical studies, other human subjects had experienced serious adverse events, and the principal investigator had a significant financial stake in the company developing the therapy [7]. Jesse's tragic death became a watershed moment, forcing a field-wide reckoning that led to intense scientific introspection and the implementation of much stricter regulatory oversight [8].

FIRST SUCCESSFUL *IN VIVO* GENE THERAPY: LEBER'S CONGENITAL AMAUROSIS

A major breakthrough occurred in 2008 with the success of an *in vivo* gene therapy for Leber's congenital amaurosis (LCA), a rare form of inherited blindness [9,10]. The treatment involved a subretinal injection of a recombinant adeno-associated virus (AAV) carrying a functional *RPE65* gene. The therapy was highly effective, and because the subretinal space is immunologically privileged, patients did not suffer from significant immune reactions.

The AAV vector proved to be an ideal delivery vehicle. It is less immunogenic than adenovirus, and its linear genome can be almost entirely replaced with a transgene. Its integration into the host genome is minimal compared to retroviral vectoral vectors, remaining predominantly episomal, though integration at DNA break sites has been documented. The therapy, later named voretigene neparvovec (Luxturna), was highly effective, providing life-changing benefits by restoring functional vision to patients with near-total blindness. It was approved by the FDA in 2017 and the EMA in 2018.

FIRST *IN VIVO* GENE THERAPY APPROVAL AND FIRST COMMERCIAL WITHDRAWAL: GLYBERA

Alipogene tiparvovec (Glybera) was a gene therapy for lipoprotein lipase (LPL) deficiency, a rare disorder caused by biallelic mutations in the *LPL* gene. It used an AAV vector to deliver a hyperfunctional variant of the *LPL* gene via multiple intramuscular injections [11,12]. The therapy reduced the frequency of pancreatitis without major adverse events and received clinical approval from the EMA in 2012, making it the first *in vivo* gene therapy approved in the Western world.

Despite its clinical promise, Glybera was a commercial failure. Its million-dollar price tag for a one-time treatment proved prohibitive. Only one person received the drug commercially before the company abandoned its marketing authorization in 2017. The remaining three doses were given to patients with a nominal price of one euro.

FIRST COMMERCIALLY SUCCESSFUL GENE THERAPY: ZOLGENSMA

Onasemnogene abeparvovec (Zolgensma) is an AAV-mediated gene therapy for spinal muscular atrophy (SMA), a devastating neuromuscular disorder caused by the absence of the *SMN1* gene [13]. First approved by the FDA in 2019, it has since become a global blockbuster.

Delivered as a single intravenous infusion, Zolgensma is a systemic *in vivo* gene therapy that provides a functional copy of the *SMN1* gene to motor neurons. To enhance its efficacy, the transgene was packaged in a self-complementary form, enabling more efficient expression. Despite its multi-million-dollar price, more than 3,700 babies with SMA have been treated. Its use, however, remains restricted to children under two years of age, as its safety and efficacy have not been formally established in older patients.

FIRST SERIOUS IMMUNE REACTION TO A TRANSGENE: DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) has long been a target for gene therapy. The *dystrophin* gene, which is defective in DMD, is too large to fit into an AAV vector. Researchers cleverly engineered a miniaturized version, microdystrophin, that could be packaged for delivery.

Several companies advanced clinical trials using AAV-mediated systemic delivery of microdystrophin. They were delivered intravenously as the primary target is skeletal muscles of the whole body and cardiac muscle. However, the high vector doses in older children led to numerous serious adverse events, including atypical hemolytic uremic syndrome, thrombotic microangiopathy, and, most recently, fatal liver failure. A particularly concerning side effect was transgene-induced myositis [14].

In a remarkable act of collaboration, competing companies shared their data to investigate the cause of myositis. They discovered that specific regions of the microdystrophin transgene were highly immunogenic, triggering a T-cell response in boys whose own mutations resulted in the complete absence of those corresponding regions in their native dystrophin protein [15].

FIRST GENE-EDITING THERAPY: CASGEVY

Exagamglogene autotemcel (Casgevy) is the first approved therapy based on CRISPR gene editing. It is an *ex vivo* treatment for beta-thalassemia and sickle cell disease. The process involves collecting a patient's hematopoietic stem cells, using electroporation to deliver the CRISPR-Cas9 system that disables the *BCL11A* gene. This gene acts as a switch that turns off fetal hemoglobin production after birth. By disabling it, the edited cells are induced to reactivate the production of functional fetal hemoglobin. After the patient undergoes myeloablative chemotherapy to clear their bone marrow, the edited cells are reinfused [16].

While often hailed as a personalized treatment, the gene-editing strategy itself is uniform, targeting the same *BCL11A* gene in all patients to achieve a common therapeutic outcome.

CONCLUSION: HURDLES AND HOPES

The landmarks detailed above represent a fraction of the events that have shaped the field of gene therapy. Significant hurdles remain, including the prohibitive cost of treatments, the challenge of conducting trials for ultra-rare disorders, and the need to tame the immune response to vectors and transgenes. Neutralizing antibodies can prevent initial treatment or re-dosing, and the long-term durability of these therapies remains unknown.

More challenges will undoubtedly emerge. Nevertheless, the relentless progress in this field signals an unwavering commitment to fighting against genetic determinism and offering hope where there was none.

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Silver–Russell Syndrome: From Molecular Pathogenesis to Clinical Management

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Silver–Russell syndrome (SRS) is a rare imprinting disorder characterized by prenatal and postnatal growth retardation, relative macrocephaly, prominent forehead, body asymmetry, and feeding difficulties. The estimated incidence ranges from 1 in 30,000 to 1 in 100,000 live births. Diagnosis is primarily clinical, supported by the Netchine–Harbison Clinical Scoring System (NH-CSS), while molecular confirmation is achieved in approximately 60% of cases. The two major genetic mechanisms are loss of methylation (LOM) at chromosome 11p15 and maternal uniparental disomy for chromosome 7 (upd(7)mat); rarer causes include abnormalities involving chromosomes 14q32, 20, and 16, or mutations in CDKN1C or IGF2. Management focuses on optimizing nutrition, preventing hypoglycemia, and addressing growth failure. Growth hormone (GH) therapy effectively improves height, body composition, and appetite in most patients, though partial IGF-1 resistance may occur, particularly in 11p15 LOM. Puberty often begins early and progresses rapidly, contributing to compromised final height; combined GH and GnRH analogue therapy may be beneficial in selected cases. Long-term follow-up is required to monitor metabolic outcomes and support individualized care based on molecular subtype. A multidisciplinary approach remains essential to address the complex endocrine, nutritional, and developmental challenges of SRS throughout childhood and adolescence.

Key words: Silver-Russell syndrome, Imprinting disorder, Uniparental disomy, Growth hormone

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INTRODUCTION

Silver–Russell syndrome (SRS, also referred to as Russell–Silver syndrome; OMIM #180860) is a rare but well-defined growth disorder characterized by both prenatal and postnatal growth retardation. The condition was independently reported by Silver et al. [1] and Russell [2], who described children presenting with low birth weight, short stature after birth, distinctive facial features, and body asymmetry. Nearly all affected infants are born small for gestational age (SGA). Affected individuals typically present with relative macrocephaly — defined as a head circumference at least 1.5 standard deviations (SD) above the birth weight and/or length — and a prominent forehead with frontal bossing, often accompanied by body asymmetry [3]. Following birth, most patients continue to exhibit postnatal growth failure, sometimes with progressive discrepancies in limb length and feeding difficulties. Additional recognizable clinical traits include a triangular facial appearance, clinodactyly of the fifth finger, and micrognathia with a narrow chin [4]. In the absence of treatment, the average adult height in individuals with SRS is approximately -3.1 SD below the population mean. The clinical presentation of SRS varies widely—from severe forms with marked growth restriction and dysmorphic features to mild cases with subtle findings. Because of this broad phenotypic spectrum, many affected individuals, especially those with extreme or attenuated features, are likely underdiagnosed or misclassified. Diagnosis often depends heavily on the clinician's experience, particularly since characteristic fea-

tures tend to become less apparent in adulthood.

Globally, the estimated incidence of SRS varies between 1 in 30,000 and 1 in 100,000 live births. A molecularly confirmed study from Estonia in 2015 suggested an incidence of approximately 1 in 70,000 [5], although this may underestimate the true prevalence due to underdiagnosis. Overall, SRS likely occurs more frequently than previously assumed, but the exact incidence remains uncertain. To address diagnostic uncertainty, several scoring systems have been developed, each using defined clinical criteria that improve the detection rate of molecular abnormalities.

DIAGNOSIS

Clinical diagnosis

Molecular analyses can confirm the diagnosis in approximately 60% of affected individuals, therefore, SRS remains primarily a clinical diagnosis, established through a combination of characteristic phenotypic findings. Identification of the molecular subtype enables more precise classification of patients and may facilitate individualized management strategies [6]. Nevertheless, in a considerable subset of clinically typical cases, molecular results are negative. To improve diagnostic consistency, multiple clinical scoring systems have been proposed over time, each reflecting the inherent difficulty of achieving a confident diagnosis [7,8].

The Netchine–Harbison Clinical Scoring System (NH-CSS) provides a validated and sensitive diagnostic framework [8]. The NH-CSS demonstrated superior diagnostic sensitivity (98%) compared with previously published scoring systems and exhibited the highest negative predictive value (89%), indicating that individuals who meet fewer than four of the six criteria are very unlikely to have SRS (Table 1).

A clinical diagnosis can be made when a patient meets at least four of the six NH-CSS criteria, which must include relative macrocephaly and prominent forehead/frontal bossing at

Table 1. Adapted Netchine–Harbison Clinical criteria for Silver–Russell syndrome

Clinical Feature	Operational Definition
Small for gestational age (SGA)	Birth weight and/or length ≤ –2 SD for gestational age.
Postnatal growth retardation	Height at age 2 ± 1 year ≤ –2 SD, or at least 2 SD below mid-parental target height.
Relative macrocephaly at birth	Head circumference at birth ≥ 1.5 SD above birth weight and/or birth length SD score.
Prominent forehead	Forehead clearly projecting beyond the facial plane on lateral view during early childhood (ages 1–3 years).
Body asymmetry	Limb length discrepancy (LLD) ≥ 0.5 cm or arm asymmetry, or LLD < 0.5 cm with at least two other asymmetric body parts (excluding face).
Feeding difficulties and/or low BMI	BMI ≤ –2 SD at 2 years of age, or current need for nutritional support (e.g., feeding tube or appetite stimulant such as cyproheptadine).

Table 2. Genetic subtypes and testing strategies in Silver–Russell syndrome
(adapted from Saal HM et al., GeneReviews®, 2025)[36].

Analytical Method	Chromosomal Region / Gene Involved	Detected Alterations	Approximate Detection Rate in SRS
Methylation testing	Chr 11p15	Hypomethylation of *H19/IGF2* imprinting control region (paternal allele)	~35%–65%
		Somatic mosaicism or partial upd(11)mat	Rare
		Maternal duplication of 11p15.5	Uncertain frequency
	Chr 7	Maternal uniparental disomy [upd(7)mat]	~5%–10%
		Segmental deletions/duplications or mosaic trisomy 7	Rare
Chromosomal microarray (SNP-based)	Chr 11p15	Maternal 11p15 duplication or somatic mosaicism for upd(11)mat	Rare
	Chr 7	Deletions, duplications of 7p, or mosaic trisomy 7	Rare
		upd(7)mat (maternal isodisomy)	~5%–10%
STR marker analysis	Chr 11p15	Somatic mosaicism for upd(11)mat	Rare
	Chr 7	upd(7)mat or maternal mosaic trisomy 7	~5%–10%
Karyotype	Chr 11p15	Structural rearrangement (e.g., inversion or translocation)	Rare
Gene sequencing/deletion–duplication testing	*CDKN1C* (maternal transmission)	Gain-of-function mutation	Rare
	IGF2 (paternal transmission)	Loss-of-function mutation	Rare
	PLAG1, HMGA2	Pathogenic variants or copy-number changes	Rare

birth, along with two or more additional features, provided that other potential syndromic causes have been excluded [8].

Molecular diagnosis

A positive molecular finding serves as a valuable means of confirming the clinical diagnosis and allows for classification into defined molecular subtypes, which can subsequently inform personalized management strategies. Nevertheless, molecular testing is often requested for individuals who display only limited or atypical features of Silver–Russell syndrome, resulting in low diagnostic yield and unnecessary financial burden for both patients and healthcare systems [4]. To date, an identifiable molecular etiology is found in roughly 60% of clinically diagnosed patients. The two major pathogenic mechanisms include loss of methylation (LOM) at chromosome 11p15 (30%–60% of cases) and maternal uniparental disomy for chromosome 7 (upd(7)mat) (approximately 5%–10% of cases) [9,10]. In the remaining patients, the molecular basis is still unclear (Table 2).

Chromosome 11p15

Both SRS and the overgrowth disorder Beckwith–Wiedemann syndrome (BWS) arise from epigenetic and structural abnormalities involving chromosome 11p15.5, a region that contains two distinct imprinted domains. The telomeric domain, which plays a major role in the pathogenesis of SRS, is regulated by the paternally methylated H19/IGF2 intergenic differentially methylated region (H19/IGF2 IG DMR) — previously referred to as IC1, ICR1, or the H19 DMR [11,12]. In contrast, the centromeric domain includes the KCNQ1OT1 TSS-DMR, also known as IC2, ICR2, LIT1, or KvDMR1 [13]. The paternally expressed IGF2 encodes a growth factor essential for fetal development and somatic growth, whereas the maternally expressed H19 produces a long noncoding RNA (lncRNA) whose biological function remains incompletely understood. When hypomethylation occurs at the H19/IGF2 IG DMR, it leads to decreased paternal expression of IGF2 and up-regulation of maternal H19, ultimately resulting in growth restriction, a hallmark of SRS.

Numerous copy-number variants (CNVs) have also been identified within the 11p15.5 locus; the resulting phenotype depends on the size, genomic content, and parental origin of each CNV [14]. Accurate diagnosis therefore requires quantitative assessment of CpG methylation within the H19/IGF2 IG DMR.

This can be achieved through bisulfite-based assays or enzymatic techniques, such as methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) and, less commonly, Southern blotting [15]. Among these, MS-MLPA is the most widely used clinical test, as it is DNA-efficient, cost-effective, and capable of simultaneously evaluating both copy number and methylation status [16].

However, hypomethylation in SRS is often partial, and low-level changes may escape detection. Furthermore, methylation levels can differ among tissues—for example, between blood leukocytes, buccal epithelial cells, and skin fibroblasts—which may account for false-negative molecular results when only blood is analyzed [17].

Although MS-MLPA can identify CNVs, genome-wide array analysis remains valuable for defining the exact size and gene composition of such rearrangements.

Chromosome 7

Cytogenetic analyses have revealed several structural abnormalities of chromosome 7 in individuals with SRS, including duplications of 7p11.2–p13 and small marker chromosomes [18]. The first molecular evidence linking chromosome 7 to SRS came from the discovery of maternal upd(7)mat, identified in approximately 10% of affected patients [19]. Microsatellite analyses in nearly all upd(7)mat cases supported a trisomic rescue mechanism as the origin. Because of this trisomic origin, it has been proposed that mosaic trisomy 7 may contribute to SRS pathogenesis. In cases of UPD, homozygosity for pre-existing recessive variants can also result in abnormal phenotypes. Indeed, upd(7)mat was first reported in a growth-restricted patient with cystic fibrosis, in whom both alleles of the CFTR mutation were inherited from the mother [20]. Nonetheless, the lack of a shared isodisomic region among SRS cases excludes a single recessive gene as the primary cause of the syndrome. The prevailing explanation for the SRS phenotype in upd(7)mat carriers is a disturbed expression of imprinted genes on chromosome 7. Upd(7)mat is consistently associated with growth retardation and SRS-like features, whereas paternal upd(7) does not produce this phenotype [19,20]. It is therefore hypothesized that reduced activity of paternally expressed genes, or alternatively overexpression of maternally expressed factors, underlies the growth restriction observed in SRS. Research has focused primarily on two candidate regions on chromosome 7: 7p11.2–p13 and 7q32 [21]. Duplications of the 7p11.2–p13 segment have been identified in SRS cases, and this region contains several growth-regulatory genes, including GRB10, IGFBP1, IGFBP3, PHKG1, EGFR, and GHRHR [22]. Among these, GRB10, a maternally expressed

imprinted gene with a key role in growth regulation, has been considered a strong candidate. However, point mutations or methylation defects in GRB10 have not been detected despite extensive screening, and duplications not involving this gene do not produce SRS features. Another locus of interest, 7q31, has been implicated through the identification of patients with segmental upd(7q) and intrauterine growth restriction. This region contains several imprinted genes (*MEST/PEG1*, *CPA4*, *COPG2*) and non-coding RNAs (*MESTIT*, *CIT1/COPG2IT1*), although no pathogenic variants or isolated imprinting defects have yet been confirmed [22]. Finally, while intrauterine growth restriction is also reported in upds of other chromosomes and may arise from confined placental mosaicism.

SRS like syndromes

Chromosome 14q32

Abnormalities involving the imprinted locus on chromosome 14q32 — including maternal uniparental disomy of chromosome 14 (upd(14)mat), paternal microdeletions, and hypomethylation of the DLK1/GTL2 intergenic DMR (also known as MEG3-DMR or 14q32-DMR) — lead to Temple syndrome [23].

This condition shows considerable clinical overlap with SRS, sharing features such as being born small for gestational age, postnatal growth failure, hypotonia, delayed motor milestones, and early puberty.

Among patients clinically diagnosed with SRS, a small number have been reclassified as having Temple syndrome, including 1 of 127, 2 of 85, and 1 of 26 individuals in reported cohorts.

However, the true frequency of 14q32 epigenetic abnormalities in patients fulfilling NH-CSS diagnostic criteria for SRS is still uncertain.

Chromosome 20 and 16

Maternal uniparental disomy of chromosomes 20 and 16 (upd(20)mat and upd(16)mat) has occasionally been identified in patients evaluated for prenatal and postnatal growth restriction or suspected SRS [20,24]. But their phenotypes lack core SRS characteristics such as relative macrocephaly and asymmetry.

CDKN1C and IGF2 gene

CDKN1C and IGF2, both located on chromosome 11p15, are key genes involved in the growth regulation abnormalities observed in SRS and BWS [25]. A maternally inherited gain-of-function mutation in CDKN1C has been identified in a multigenerational family with SRS, whereas a paternally inherited loss-of-function mutation in IGF2 was reported in another familial case. To date, however, no additional pathogenic variants in either gene have been found in sporadic or familial SRS cases. Therefore, sequence analysis of CDKN1C and IGF2 may be warranted mainly in familial SRS where the inheritance pattern supports such testing, although coding mutations in these genes remain rare.

MANAGEMENT

Feeding difficulties

Infants with SRS are typically shorter and lighter than peers, with weight declining further after birth because of poor appetite, feeding difficulty, and gastrointestinal problems. Persistent undernutrition can lead to calorie-related growth failure. Digestive symptoms such as reflux or constipation are frequent, and nutritional management during infancy focuses on preventing hypoglycemia and restoring growth before GH therapy begins [26]. However, excessive or forced feeding requires caution, as rapid catch-up weight gain in small-for-gestational-age children increases future metabolic risk. Because of their low muscle mass and altered body composition, SRS patients need individualized nutritional targets, balancing adequate caloric intake without over nourishment [27].

Hypoglycemia

Young children with SRS are prone to fasting hypoglycemia due to reduced muscle and liver glycogen stores, large brain-to-body ratio, and feeding difficulties, particularly under age 5 years. Regular urinary ketone testing helps determine individual fasting tolerance and guide preventive feeding strategies [28]. Nighttime hypoglycemia can be avoided by adding slow-release carbohydrates such as uncooked cornstarch to the evening feed. During illness or preoperative fasting, intravenous glucose may be necessary. Because of gastrointestinal dysmotility, reintroduction of oral or enteral feeding often requires a longer recovery period than in SGA children. Glucagon is not recommended for the treatment of hypoglycemia in these patients, as their glycogen reserves are low and their capacity for gluconeogenesis is limited. If hypoglycemia persists, early initiation of GH therapy should be considered [29].

Growth hormone treatment

Data on final height in untreated individuals with SRS are

scarce, but most achieve an adult height around −3 SDS. SRS is recognized as an indication for GH therapy under the SGA indication license, and clinical trials including SRS patients supported the FDA (food and drug administration) and EMA (European medicines agency) approvals in the early 2000s [30]. Subsequent studies have shown that children with SRS exhibit a growth response to GH comparable to that of non-syndromic SGA children, with mean total height gains of approximately +1.2 to +1.4 SDS, corresponding to an improvement of 7–11 cm in predicted adult height [31]. Although final height tends to remain lower in SRS, all molecular subtypes benefit from GH therapy, particularly when started at a younger age and lower baseline height SDS.

Consensus guidelines recommend early GH therapy for children with SGA, including those with SRS, when height is ≤−2.5 SDS at 2–4 years of age and the dose is 35–70 μg/kg/day [32]. Beyond promoting linear growth, GH can enhance appetite, lean body mass, and muscle strength, similar to its effects in Prader–Willi syndrome. Although classic GH deficiency is uncommon in SRS, treatment typically increases height velocity by ≥3 cm/year. Children with 11p15 LOM often show elevated IGF-1 and IGFBP-3 levels, suggesting partial IGF-1 resistance, which complicates biochemical monitoring during therapy. Overall, GH treatment is considered safe and effective in SRS, with no higher risk of adverse effects than in non-syndromic SGA children.

Advanced skeletal maturation

Data on bone age progression in SRS are limited, but early bone age delay is typically followed by rapid advancement around 8–9 years of age, often earlier in overnourished children [33]. Puberty generally begins within the normal range but tends to occur earlier and progress faster than in non-syndromic SGA peers, particularly in those with 11p15 LOM or upd(7)mat. Accelerated bone maturation and a rapid pubertal tempo contribute to reduced pubertal growth and lower adult height. Combined therapy with GH and gonadotropin-releasing hormone analogues (GnRHa) may help improve final height in selected patients with early puberty, although results remain inconsistent [34]. Aromatase inhibitors such as anastrozole are being investigated as potential options to slow bone maturation in SRS, but their use is not yet approved for growth disorders.

Metabolic complications

Individuals born SGA have an increased risk of metabolic syndrome in adulthood, particularly when rapid or disproportionate postnatal weight gain occurs. In SRS, insulin resistance may be subtle in prepubertal children but becomes more evident during puberty, occasionally progressing to glucose intolerance or type 2 diabetes [35]. Although GH therapy generally improves body composition and lipid metabolism in SGA populations, specific data in SRS remain limited. Children with 11p15 LOM appear to have higher metabolic risk than those with upd(7)mat, likely due to reduced muscle mass and elevated IGF-1 levels. Long-term studies are needed to clarify genotype-specific metabolic effects of GH treatment in SRS.

CONCLUSION

Children with SRS encounter diverse medical and developmental challenges from infancy to adulthood. Beyond the general complications of being born SGA, key management concerns include feeding difficulties, postnatal growth failure, recurrent hypoglycemia, early adrenarche and puberty, insulin resistance, body asymmetry, dental and airway problems, and other congenital anomalies. These recommendations apply to all clinically diagnosed cases, but molecular subtype identification can help tailor management according to specific risks. Optimal care requires a multidisciplinary approach and active family involvement.

AUTHOR CONTRIBUTIONS

This study was designed and the manuscript was written by Kyungmi Jang. Jungeun Moon contributed to the revision and editing of the manuscript.

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Apolipoprotein E: Linking Lipid Metabolism, Alzheimer's Disease, and Therapeutic Innovation

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Lipoproteins and apolipoproteins are essential macromolecules that maintain systemic lipid homeostasis and cellular energy balance by transporting lipids through plasma and interstitial fluids. Structurally, lipoproteins consist of hydrophobic lipid cores surrounded by amphipathic apolipoproteins, which determine their metabolic fate, receptor interactions, and physiological functions. Among apolipoproteins, apolipoprotein E (APOE) plays critical roles in lipid transport, nerve repair, and immune regulation. APOE encoded by *APOE* gene (OMIM*107741) exists in three common isoforms (APOE2, APOE3, and APOE4), which differ by cysteine/arginine substitutions at residues 112 and 158. These subtle structural changes profoundly alter receptor binding affinity, lipidation efficiency, and protein stability, resulting in distinct metabolic and pathological outcomes. In particular, APOE4 is the strongest genetic risk factor for late-onset Alzheimer's disease (AD). APOE4 promotes amyloid-β (Aβ) aggregation, impairs Aβ clearance, enhances tau hyperphosphorylation, and triggers neuroinflammatory signaling. APOE-mimetic peptides, designed to replicate key functional domains of the native protein, exhibit neuroprotective, anti-inflammatory, and lipid-modulatory effects in preclinical models of AD, stroke, and atherosclerosis. Concurrently, advances in *APOE* genotyping are expanding clinical applications in AD risk prediction, lipid-lowering therapy, and personalized prevention. Understanding the molecular mechanisms and clinical relevance of the *APOE* gene remains essential for translating genetic insights into therapeutic and diagnostic innovation across metabolic and neurodegenerative diseases. This review highlights the *APOE* gene as a pivotal link between lipid metabolism and neurodegeneration. Integration of recent advances in its structural variants, disease mechanisms, therapeutic modulation, and clinical genotyping underscores the importance of *APOE* as both a biomarker and a therapeutic target.

Key words: Apolipoproteins E, Alzheimer's disease, APOE-mimetic peptide, Lipoproteins

REVIEW ARTICLE

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INTRODUCTION

Lipid metabolism is increasingly recognized as a central determinant of both neurological health and peripheral metabolic process. Lipoproteins, which are macromolecular complexes composed of a lipid core, are essential for the systemic transport of cholesterol and triglycerides through the circulatory system [1]. In addition to their role in peripheral lipid homeostasis, lipoprotein-associated apolipoproteins influence the structure and function of the central nervous system (CNS) through membrane maintenance, lipid trafficking, and signaling [2,3]. Among apolipoproteins, apolipoprotein E (APOE) occupies a unique position in linking peripheral lipid transport to neurobiological processes such as synaptic remodeling, inflammatory regulation, and neuronal repair [2-4].

This review integrates the latest insights into lipoprotein and apolipoprotein biology, with a particular focus on APOE and its role in Alzheimer's disease (AD).

Lipid, Lipoproteins, and Apolipoproteins

Lipids, whether synthesized endogenously or absorbed from the diet, must be transported to various tissues to fulfill their metabolic functions. In the plasma, they are carried within macromolecular complexes known as lipoproteins, which are lipid-protein complexes. Lipoproteins contain one or more specific proteins,

called apolipoproteins, located on their surface. The structure of core lipids with the overlying phospholipids, cholesterol, and apolipoprotein coat is stabilized by noncovalent forces. This interaction is sufficiently loose to permit the rapid spontaneous exchange of cholesterol, which is more water-soluble than the other lipids, between plasma lipoproteins and cell membranes [1,4].

Lipoproteins are synthesized in the liver and intestines, derived from metabolic modification of precursor lipoproteins, or assembled into cell membranes from cellular lipids and exogenous lipoproteins or apolipoproteins. In the circulation, lipoproteins are highly dynamic. They undergo enzymatic modifications of their lipid components, facilitated and spontaneous lipid exchange, the transfer of soluble apolipoproteins, and structural changes in the apolipoproteins in response to changes in composition. Ultimately, lipoproteins are taken up and catabolized by the liver, kidney, and peripheral tissues via receptor-mediated endocytosis and other mechanisms [1,4].

Although the assembly, structure, metabolism, and receptor interactions of lipoproteins are largely governed by their apolipoprotein components, lipoproteins are most commonly classified according to their hydrated density or electrophoretic mobility on agarose gel. They are categorized into six major classes based on hydrated densities: chylomicron, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein(a). Each class contains a distinct combination and proportion of apolipoproteins [1,5].

Apolipoproteins are the protein components of lipoprotein particles, serving as structural scaffolds, enzyme cofactors, and receptor ligands. The prefix, "apo" derived from Greek, means "away from". Structurally, apolipoproteins are generally amphipathic proteins: hydrophobic regions interacting with lipid surfaces and hydrophilic residues exposed to aqueous surroundings. There properties enable the solubilization, transport, and metabolism of lipids in the blood and cerebrospinal fluid and are essential for the formation, stabilization, remodeling and clearance of lipoprotein particles [3,4]. However, their complete functions are not yet clear. Apolipoproteins are categorized based on their structure, genetic origin, and functional role in lipoprotein metabolism. They are primarily divided into five main classes: A, B, C, D, and E, each with several subtypes [5].

Among these, APOE plays a crucial role in neural growth, remyelination, and nerve regeneration. It is a 34-kDa plasma glycoprotein composed of 299 amino acids, encoded by the gene *APOE* (19q13.2, MIM*107741) in human. It is found on all lipoproteins, but only a small amount is on LDL. Lipoproteins containing APOE are removed from circulation by several different cellular receptors that recognize a positively charged amino acid cluster in a specific region of the protein. APOE facilitates hepatic uptake of lipoproteins by interacting with a variety of receptors, such as the chylomicron remnant receptor, low-density lipoprotein receptor, and LDL receptor-related protein [6-8].

APOE exists in three common isoforms, APOE2, APOE3, and APOE4, distinguished by amino acid substitutions at residues 112 and 158, which correspond to the three allelic variants of the *APOE* gene, ε2, ε3, and ε4, respectively [3,4]. These isoforms can be differentiated by isoelectric focusing electrophoresis:

- APOE2 encoded by *APOE* ε2, contains cysteine at both positions 112 and 158.
- APOE3 encoded by *APOE* ε3, has cysteine at 112 and arginine at 158.
- APOE4 encoded by *APOE* ε4, contains arginine at both positions.

These isoforms differ in their biophysical properties, receptor-binding affinities, and regulatory effects on lipid and energetic homeostasis [2]. APOE2 has a reduced binding affinity for the B and/or E remnant receptor compared with APOE3, which can lead to the accumulation of lipoprotein in the plasma. Conversely, APOE4-containing lipoproteins are cleared more rapidly than those containing APOE3 but can disrupt lipid homeostasis through altered receptor recycling and lipid trafficking [3,6].

Among *APOE* alleles, ε3 is the most prevalent globally, although allele frequencies vary among populations. These genetic variants contribute substantially to interindividual variability of LDL-cholesterol and ApoB-100 concentrations. Because ApoB-100 is the major apolipoprotein of LDL, its plasma concentration serves as a surrogate marker for LDL particle number [1]. Individuals carrying at least one ε2 allele generally exhibit lower ApoB-100 and LDL- cholesterol levels than ε3 homozygotes, while carriers of at least one ε4 allele tend to show higher concentrations. This is likely due to increased hepatic uptake of lipoproteins in ε4 carriers, leading to hepatic cholesterol accumulation and subsequent downregulation of the LDL receptor expression [5,6].

APOE genotype and AD

AD is a progressive neurodegenerative disorder character-

ized by cognitive decline, synaptic dysfunction, and neuronal loss, accompanied by the accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Genetic, biochemical, and neuropathological evidence indicates that APOE significantly influences the risk, onset, and progression of late-onset AD [7,9].

Among the three major APOE isoforms, *APOE* ε4 allele is the strongest known genetic risk factor for late-onset AD, while APOE ε2 confers relative protection compared with the neutral APOE ε3 allele. Individuals carrying one copy of the ε4 allele (heterozygotes) have a 3- to 4-fold increased risk of developing AD, whereas those homozygous for ε4 have a 10- to 15-fold higher risk compared to ε3 homozygotes. In contrast, the ε2 allele appears to decrease AD risk and delay onset. APOE4-associated risk is observed in both sexes but tends to be more pronounced in females [7,9-16].

Recent transcriptomic and functional studies demonstrate that APOE4 reshapes cellular and molecular networks even in asymptomatic individuals, influencing brain aging trajectories and predisposing to neurodegeneration [13,14,17-19]. Although the precise mechanisms linking *APOE* gene to AD pathogenesis remain incompletely defined, they likely involve direct and indirect interactions with Aβ plaques and tau tangles—the pathological hallmarks of the disease [13,17].

Mechanisms: Lipid Metabolism, Aβ, Tau, and Neuroinflammation

Lipidation & Astrocyte Function: APOE4 disrupts astrocytic lipid metabolism, promoting the secretion of triglyceride-rich, poorly lipidated lipoprotein particles instead of cholesterol-rich high-density lipoproteins. This alteration impairs lipid clearance and promotes intracellular lipid accumulation, astrocyte dysfunction, and lipotoxic stress [18,19].

Amyloid β (Aβ) Pathology: APOE4 can directly bind to and alter the lipid microenvironment, thereby reducing Aβ clearance, promoting aggregation, and facilitating the formation of more toxic oligomers [11,17].

Tau Pathology: APOE4 enhances tau hyperphosphorylation and neurofibrillary tangle accumulation. Humanized mouse and iPSC-derived models demonstrated that trans-synaptic spread and cytoskeletal instability are accelerated depending on sex and age [7,20].

Microglial Dysfunction & Neuroinflammation: APOE4 reprograms microglial lipid metabolism, increasing lipid droplet accumulation, cholesterol overload, lysosomal impairment, and activating NF-κB and type-I interferon signaling. These changes reduce phagocytosis of Aβ, tau, and synaptic fragments, exacerbate neuroinflammation, and impair neuron–microglia interactions [12,21].

Brain Structure & Cognition: Cognitively normal individuals carrying ε4 allele experience brain microstructure changes, including decreased entorhinal neurite density and diffusion MRI changes [22].

Vascular/Redox and Ferroptosis Pathways: APOE4 increases neuronal vulnerability by affecting blood–brain barrier integrity, oxidative stress, lipid peroxidation, and ferroptosis [7].

APOE4's multifactorial roles have prompted therapeutic strategies beyond Aβ targeting approaches, including modulation of lipidation, correction of microglial lipid metabolism, mitigation of endoplasmic reticulum stress, and attenuation of inflammatory signaling [21]. However, measuring total APOE concentration in plasma or CSF is not enough as a diagnostic marker. The total concentration often does not reliably distinguish AD from non AD patients and does not always correlate with genotype or disease state [8,23]. However, isoform-specific quantification of APOE in CSF and plasma, combined with longitudinal monitoring of isoform ratios, may refine risk stratification and treatment response prediction [10,24]. In addition, personalized risk assessment increasingly integrates *APOE* genotype, sex, age, and metabolic context [10,13,21]. Notably, some anti-Aβ therapies exhibit differential efficacy or safety profiles in *APOE* ε4 carriers—for instance, higher incidence of amyloid-related imaging abnormalities in those with ε4 genotype [12,25]. Environmental and metabolic factors including metabolic stress, lipid dysregulation, and diet, are more influential on APOE4 toxicity. For example, astrocytes under stress produce more harmful lipid particles when expressing APOE4 [10].

Despite considerable progress, several key questions regarding APOE4's role in AD remain unresolved. First, the precise mechanisms by which APOE4 modulates tau propagation in humans require further clarification [26]. Second, it remains to be determined at which disease stages, and to what extent, altering APOE4 expression, lipidation status, or functional activity can actually reverse or slow pathology in human subjects [27]. Third, the relative contributions and therapeutic accessibility of peripheral versus central pools of APOE are not well understood—such as whether modulating brain-derived APOE or circulating APOE (or both) yields safer or more effective interventions. Finally, more detailed longitudinal human studies are needed, including tracking of APOE isoform ratios, markers of lipid metabolism, microglial function, and other

biomarkers, to distinguish causal drivers from downstream effects in the pathophysiology of AD [28].

Clinical Utility of *APOE* genotype testing

Although *APOE* genotyping was once primarily confined to research, it is increasingly applied to AD risk stratification, prognostic assessment, and therapeutic planning [13,16,25]. When combined with complementary tools, such as biomarkers, neuroimaging, and cognitive assessment, *APOE* genotyping enhances diagnostic accuracy. However, *APOE* genotyping has several limitations, including its incomplete predictive power - many ε4 carriers do not develop AD, while some non-carriers can still progress. Moreover, there are ethical concerns, such as potential discrimination and psychological stress, further complicate its use. Pharmacogenetic associations, e.g., response to statins or omega-3 fatty acids, remain inconsistent and lack clear clinical significance. Therefore, clinical implementation of *APOE* genotyping must carefully address ethical, interpretive, and logistical challenges, particularly in asymptomatic individuals.

Overall, *APOE* genotyping is most valuable for clinical trial stratification, biomarker-supported diagnostics, and individualized risk assessment, but it is not recommended as a standalone diagnostic test or for population-wide screening.

APOE-mimetic peptides: Mechanisms and therapeutic potential

There has been growing interest in therapeutic strategies that modulate APOE function. One promising approach involves APOE-mimetic peptides. In animal models of AD and acute CNS injury, APOE-mimetics have demonstrated efficacy in improving behavior, reducing amyloid and tau pathology, suppressing inflammation, and enhancing neuronal survival [15, 29,30].

APOE-mimetics are short peptides derived from functional motifs of the APOE protein, particularly receptor-binding and anti-inflammatory domains. Most APOE-mimetics mimic the receptor-binding domain of APOE protein (amino acids 141–149), facilitating interactions with members of the LDL receptor family. They also promote APOE lipidation via ABCA1 transporters, which enhances lipid trafficking and amyloid clearance in the brain. These peptides have been shown to shift amyloid precursor protein processing towards the non-amyloidogenic α-secretase pathway, thereby reducing Aβ production [31-34] (Table 1).

APOE-mimetic peptides show therapeutic promise in reducing Aβ and tau pathology, as well as improving cognition—evidenced by CS-6253 treatment in APOE3 mice, which increased APOE lipidation, lowered soluble and insoluble Aβ, reduced amyloid deposits, and improved memory when given before pathology onset. They have also been shown to attenuate neuroinflammation: in transgenic AD models, administration of APOE receptor-binding region peptides led to reduced inflammatory cytokines (e.g. IL-6), fewer plaque and tangle pathologies, and improved behavior. In dyslipidemia and metabolic disorder settings, the lipid-efflux-promoting action of mimetic peptides (via ABCA1 or similar pathways) yields antioxidant benefits and improved lipid handling in peripher-

Table 1. Key APOE-mimetic peptides: types, domains, and experimental findings

APOE-mimetic peptide	Feature	Key Experimental Findings
CS 6253 [31]	Small α-helical peptide derived from the C-terminal lipid-binding domain of *APOE* gene: it stabilizes ABCA1 and maintains its plasma membrane localization.	In APOE3-expressing transgenic mice, early treatment increased brain APOE levels, reduced Aβ pathology, and improved memory. Late treatment showed limited benefit.
Monomer, dimer, trimer of "LRKLRKRLL" motif [32]	Peptides containing a double or triple tandem repeat of the APOE receptor-binding region, LRKLRKRLL (residues 141–149): Binding effect increases with repeat units.	Reduced Aβ production and increased sAPP levels. Trimer peptides showed greater efficacy than monomers or dimers (trimer > dimer > monomer).
COG1410, COG112, COG133 [33]	Peptides derived from APOE receptor binding domain residues 130-150 of *APOE* gene; it bound to the SET protein which is a potent physiological inhibitor of PP2A	APOE and APOE-mimetic peptides antagonize SET, thereby enhancing endogenous PP2A phosphatase activity, which reduces levels of phosphorylated kinases, signaling, and inflammatory response. Improved cognition and reduced Aβ/tau pathology in mouse models.
Ac hE18A NH_2 and related [34]	Lipid-modulating and anti-inflammatory mimetics with modified amphipathic α-helical structures.	Lowered lipid hydroperoxide levels, reduced oxidative and inflammatory stress, promoted autophagy. Promising in models of diabetes and dyslipidemia.

ABCA1, ATP-binding cassette transporter A1; Aβ, amyloid-β; sAPP, surface amyloid precursor protein; PP2A, protein phosphatase 2A.

al and glial cells.

However, despite encouraging preclinical data, their translation to humans is still at an early stage. Human trials are lacking, and several critical issues remain unresolved: long-term safety, effective blood–brain barrier permeability, isoform-specific efficacy—especially for *APOE* ε4 carriers—and immunogenicity are not yet well characterized. Evidence also suggests that timing is crucial: the CS-6253 peptide was effective only when administered before or early in pathology in male mice that express APOE3, with little or no effect if administered later or in *APOE* ε4 animals [31].

In summary, APOE-mimetic peptides represent a novel therapeutic direction targeting lipid metabolism, amyloid/tau accumulation, and neuroinflammation in neurological and metabolic diseases. For clinical application, further investigation is required into their pharmacokinetics, isoform-specific activity, safety in humans, and optimal timing of treatment relative to disease stage.

SUMMARY

The *APOE* ε4 allele is consistently and strongly associated with increased risk of AD through multiple interconnected pathways. These include impaired Aβ clearance and enhanced aggregation, altered tau kinetics, dysregulated lipid metabolism, particularly in astrocytes and microglia, and heightened neuroinflammatory responses. Recent evidence further indicates that these effects are modulated by isoform concentration, age, sex, and environmental factors. Treatment strategies targeting these mechanisms show considerable promise, while biomarker-based studies are advancing clinical understanding of *APOE* status as a dynamic biological system rather than merely a static genetic risk factor.

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Congenital Hyperinsulinism in Infancy and Childhood: Pathophysiology, Diagnosis, and Management

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Congenital hyperinsulinism (CHI) is the leading cause of severe and persistent hypoglycemia in infants and children. Hyperinsulinemic hypoglycemia (HH) represents a clinically and genetically heterogeneous disorder, manifesting as transient forms related to perinatal stress or persistent forms caused by molecular defects in the genes regulating insulin secretion from pancreatic β-cell. Pathogenic variants in the K_{ATP} channel genes (*ABCC8, KCNJ11*) are the most frequent causes, although variants in other channels/transporter, metabolic enzymes, and transcription factors have also been reported. Syndromic forms associated multisystemic disorders also recognized. Prompt recognition of hypoglycemia, determination of its underlying etiology, and appropriate management are crucial to prevent irreversible neurodevelopmental impairment.

Key words: Hypoglycemia, Hyperinsulinism, Insulin, Diazoxide

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INTRODUCTION

Hyperinsulinemic hypoglycemia (HH) is the most common cause of persistent hypoglycemia in infants and children. Dysregulated insulin secretion results in recurrent hypoglycemic episodes and suppression of ketone body production, which are an essential alternative fuels for the brain. Because the neonatal and infant brain has particularly high glucose requirements, these metabolic disturbances pose a substantial risk of hypoglycemia induced-brain injury. Timely recognition and appropriate management of hypoglycemia are therefore critical to prevent adverse neurodevelopmental outcomes. Congenital hyperinsulinism (CHI) represents a clinically and genetically heterogeneous condition that may present as either transient or persistent. Identifying the underlying etiology of HH is essential, as it guides therapeutic decision-making and defines the need for long-term follow-up [1-3].

Insulin release from Pancreatic β-Cells

Glucose enters pancreatic β-cells and is phosphorylated by glucokinase (GCK), which functions both as a metabolic enzyme and a glucose sensor. The resulting glucose-6-phosphate undergoes glycolysis to generate pyruvate, which enters the tricarboxylic acid (TCA) cycle and promotes ATP synthesis. The resulting increase in the intracellular ATP/ADP ratio leads to closure of ATP-sensitive potassium (K_{ATP}) channels, composed of Kir6.2 and SUR1 subunits, causing membrane depolarization, opening of voltage-dependent calcium channels (VDCCs), Ca^{2+} influx, and exocytosis of insulin granules [4,5]. The ability of glucose metabolism to elevate cytosolic Ca^{2+}, and thereby insulin secretion is referred to as the 'triggering pathway' (K_{ATP}-dependent pathway). Following calcium influx, insulin release

is further augmented by several 'amplification pathways', which include mitochondria-derived signals and receptors-mediated mechanisms [6,7].

Classification of Hyperinsulinism

Hyperinsulinism (HI) presenting in the immediate neonatal period may result from either genetic or acquired causes. Despite variation in clinical features, severity of hypoglycemia, and treatment durations, all forms of HI carry a significant risk of hypoglycemia-induced brain injury. HI is broadly categorized as transient or persistent. Persistent CHI is most often genetic, whereas transient forms are typically acquired and asso-

Table 1. Principle genes involed in congenital hyperinsulinism

Genes	Inheritance	Diazoxide-responsive	Features
K_{ATP} channnel protein			
ABCC8	AR, biallelic	No	Diffuse histology
KCNJ11			LGA,
			high GIR requirement
			protein-induced hypoglycemia,
	AR, monoallelic*	No	Focal histology
			approximately 50% LGA,
			moderate-high GIR requirement
			protein-induced hypoglycemia
	AD	No	Diffuse histology
			Clinically indistinguishable recessive form
	AD	Yes	Diffuse histology
			Milder phenotype with less severe hypoglycemia, lower GIR requirement, protein-induced hypoglycemia
Ion & solute transporters			
KCNQ1	AD/AR	Yes	Diffuse histology, Hereditary long QT syndrome, deafness, gastrointestinal defects
CACANA1D	AD	Yes	Diffuse histology, Heart defect, Severe hypotonia
SLC16A1	AD	Yes	Diffuse histology, exercise induced HI
Enzyme and regulators of vesicle release			
GLUD1	AD	Yes	Diffuse histology
			Hyperinsulinemia hyperammonemia syndrome
			Protein induced hypoglycemia
GCK	AD	Variable	Diffuse /Atypical histology
			Ketotic hypoglycemia with prolonged fasting
			Variable severity and age of onset
HADH	AR	Yes	Diffuse histology
			Elevated plasma 3-hydroxybutyrylcarnitine and urinary 3-hydroxyglutaric acid.
			Protein-induced hypoglycemia
HK1	AD	Yes	Diffuse histology, isolated HI
PMM2	AR	Yes	Diffuse histology, Polycystic kidney
PGM1	AR		Diffuse histology, Postprandial and fasting hyperketotic hypoglycemmia
Transcription factor			
HNF1A	AD	Yes	Diffuse histology, Risk for Diabetes (MODY 1)
HNF4A	AD	Yes	Diffuse histology, Risk for Diabetes (MODY 3)
FOXA2	AD	Yes	Diffuse histology, Hypopituitarism
EIF2S3	X-linked	Yes	Diffuse histology, Hypopituitarism

AR, autosomal recessive; AD, autosomal dominant; K_{ATP}, adenosine triphosphate-sensitive potassium channel; LGA, large for gestational age; GIR, glucose infusion rate; *ABCC8*, ATP-Binding Cassette Subfamily C Member 8; *KCNJ11*, Potassium Inwardly-Rectifying Channel Subfamily J Member 11; *KCNQ1*, Potassium voltage-gated channel subfamily Q member 1; *CACANA1D*, Calcium voltage-gated channel subunit alpha1 D; *SLC16A1*, solute carrier family16 member 1; *GLUD1*, Glutamate Dehydrogenase 1; *GCK*, glucokinase; *HADH*, hydroxyacyl-coenzyme A dehydrogenase; *HK1*, hexokinase1; *PMM2*, Phosphomannomutase 2; *PGM1*, Phosphpglucomutase 1; *HNF4A*, hepatocyte nuclear factor 4 alpha; *HNF1A*, hepatocyte nuclear factor 1 alpha; *FOXA2*, Forkhead box A2; *EIF2S3*, Eukaryotic translation initiation factor 2 subunit gamma.
*Paternally inherited recessive mutation with somatic loss of maternal 11p15 region, resulting in paternal isodisomy, and localized β-cell proliferation.

ciated with perinatal risk factors such as maternal diabetes, birth asphyxia, intrauterine growth restriction, prematurity, erythroblastosis fetalis, maternal medications (e.g., sulfonylureas, beta-blockers), or intrapartum glucose infusion [2]. Perinatal stress–induced HI represents an exaggerated form of transitional hypoglycemia caused by hypoxia-mediated lowering of the β-cell glucose threshold for suppression of insulin secretion. Transient HI generally resolves within days to weeks but may persist for several months, and severe cases occasionally require diazoxide therapy [8,9].

Clinically, HI can also be classified according to the response to diazoxide, the first line pharmacological agent for managing hypoglycemia. Up to 90% of diazoxide-unresponsive cases harbor *ABCC8* or *KCNJ11* mutations [10], making unresponsiveness a strong indicator of an underlying genetic etiology. Based on histological features, CHI can be categorized into diffuse, focal, and atypical variants, depending on the extent and distribution of β-cell hyperplasia within the pancreas. The focal form is characterized by localized islet cell hyperplasia, the diffuse form involves the entire pancreas, and atypical CHI lacks clear features of either type [2].

Genetic etiology

Genetic forms of HI typically present in the neonatal period, although some cases may remain undiagnosed until later infancy or childhood. The estimated incidence of non-syndromic genetic HI is approximately 1 in 25,000–45,000 newborns [3]. Pathogenic variants have been identified in genes encoding pancreatic β-cell ATP-sensitive potassium (K_{ATP}) channels, other channels and transporters, enzymes, and transcription factors [2] (Table 1).

ABCC8 (ATP-Binding Cassette Subfamily C Member 8) or *KCNJ11* (Potassium Inwardly-Rectifying Channel Subfamily J Member 11)

The most common and severe form of monogenic HI results from dysfunction of the adenosine triphosphate-sensitive potassium channel (K_{ATP}) caused by inactivating mutations of the *ABCC8* or *KCNJ11* genes, which encode the SUR1 and Kir6.2 subunits of the K_{ATP} channel, respectively [11,12]. These variants may be inherited in recessive or dominant patterns.

Infants with K_{ATP}-channel mutations are typically large for gestational age, often requiring high glucose infusion rates to maintain euglycemia. Biallelic recessive mutations abolish K_{ATP} channel expression, leading to diffuse, diazoxide-unresponsive HI [13]. Monoallelic paternal recessive mutations, with combined somatic loss of the maternal 11p15 region, result in focal HI through a 'two-hit' mechanism that produces paternal uniparental disomy and localized β-cell proliferation [14,15]. Monoallelic dominant mutations permit normal channel trafficking but impair function. Variants that markedly diminish channel activity cause diazoxide-unresponsive HI, whereas those retaining partial activity may result in diazoxide-responsive. Clinically, biallelic recessive and dominant diazoxide-unresponsive K_{ATP}-HI are indistinguishable at presentation [13]. Although diffuse K_{ATP}-HI is generally diazoxide unresponsive, rare patients with compound heterozygous *ABCC8* mutations have shown diazoxide responsiveness or spontaneous remission [16-18]. Conversely, activating mutations in *ABCC8* or *KCNJ11* have the opposite effect, impairing insulin secretion and leading to neonatal diabetes or maturity-onset diabetes of the young (MODY) [19].

SLC16A1 (solute carrier family16 member 1)

The *SLC16A1* gene encodes monocarboxylate transporter 1 (MCT1), which facilitate the cellular uptake of monocarboxylate such as pyruvate and lactate. Under normal physiological conditions, *SLC16A1* expression is silenced in pancreatic β-cells to prevent inappropriate insulin secretion during anaerobic exercise. Activating promoter mutations in *SLC16A1* leads to aberrant β-cell expression of MCT1, allowing pyruvate to enter the TCA cycle, increase ATP production, and stimulate insulin release. This results in exercise induced hyperinsulinism (EIHI), characterized by hypoglycemic episodes, occurring within 3-5 min after strenuous physical activity [20].

GLUD1 (Glutamate Dehydrogenase 1)

The second most common genetic cause of CHI is activating mutations in GLUD1, which encodes glutamate dehydrogenase (GDH). These mutations impair guanosine-5′-triphosphate (GTP)-mediated inhibition of GDH, leading to increased conversion of glutamate to α-ketoglutarate and ammonia. The enhanced entry of α-ketoglutarate into the TCA cycle increases ATP production, thereby stimulating inappropriate insulin secretion. GDH activity is physiologically inhibited by GTP and short chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD), and allosterically activated by leucine, explaining the protein- and fasting induced hypoglycemia seen in these patients [2,6,13]. Most cases are mild and diazoxide responsive. Affected individuals typically present late infancy with hyperinsulinism–hyperammonemia (HI/HA) syndrome [21], characterized by postprandial hypoglycemia after protein-rich meals, fasting hy-

poglycemia, with moderate elevated plasma ammonia, increased urinary α-ketoglutarate. Seizures, learning disabilities, and attention deficit hyperactivity disorder are also observed [2,6,13,21].

GCK (Glucokinase)

GCK catalyzes the phosphorylations of glucose to glucose-6-phosphate, thereby entering glycolysis and promoting ATP production, which subsequently triggers insulin secretion. Activating mutations in *GCK* lower the glucose threshold for insulin release, causing hyperinsulinemic hypoglycemia of variable severity [22]. The response to diazoxide is variable. Affected individuals may develop ketotic hypoglycemia during prolonged fasting, in contrast to the hypoketotic hypoglycemia characteristic of other forms of HI [23]. Conversely, inactivating mutations in *GCK* reduce β-cell glucose sensitivity and cause neonatal diabetes or maturity-onset diabetes of the young (MODY) [19].

HADH (Hydroxyacyl-CoA Dehydrogenase)

HADH encodes SCHAD, an enzyme that normally exerts an inhibitory effect on GDH. Biallelic loss of function mutation in *HADH* impair this inhibition, resulting in increased GDH activity, enhanced ATP production, and inappropriate insulin secretion. The clinical phenotype resembles GDH-HI, presenting with fasting- and protein-induced hypoglycemia but without hyperammonemia. Disease severity is variable, ranging from severe neonatal CHI to later-onset, protein-sensitive, diazoxide-responsive forms. Characteristic biochemical features may include elevated plasma 3-hydroxybutyrylcarnitine and urinary 3-hydroxyglutaric acid [24].

HK1 (hexokinase1)

HK1 encodes a glycolytic enzyme that catalyse the phosphorylation of glucose to glucose 6 phosphate. It is broadly expressed across most tissues but is normally silenced in the liver and pancreatic β-cell. Activating mutations in non-coding regulatory regions of *HK1* cause loss of gene repression, leading to inappropriate β-cell expression of hexokinase and dysregulated insulin secretion, resulting in HI [25]. Most affected individuals respond to diazoxide [3].

HNF4A (hepatic nuclear factor 4 alpha) and *HNF1A* (hepatic nuclear factor 1 alpha)

Dominant Inactivating mutations in *HNF4A* and *HNF1A* cause diazoxide-responsive form HI, often presenting with neonatal hypoglycemia that resolves during early childhood [26]. These transcription factor variants are also well-recognized causes of MODY (MODY1 and MODY3), and affected individuals remain at risk of diabetes later in life, even when neonatal HI is transient. In families with a history suggestive of MODY, genetic testing for *HNF1A* and *HNF4A* is recommended [3].

Syndromic forms

In a small portion of CHI cases, HI occurs occurs as part of syndromic or multisystemic diseases. including overgrowth syndromes (e.g. Beckwith-Wiedemann and Sotos syndromes), chromosomal and monogenic developmental syndromes with postnatal growth failure (e.g. Turner syndromes, Kabuki syndromes, and Costello syndromes), congenital disorders of glycosylation, and syndromic channelopathies (e.g. Timothy syndrome). The underlying HI mechanisms in these conditions remain unclear, and the metabolic abnormalities are transient [27].

DIAGNOSIS

Diagnosis of CHI is based on clinical presentation and characteristic biochemical findings obtained during hypoglycemia. Evidence of excessive insulin action at the time of hypoglycemia (plasma glucose <50 mg/dL) include suppressed plasma β-hydroxybutyrate (<1.8 mmol/L), free fatty acids (<1.7 mmol/L), an inappropriately large glycemic response to glucagon (≥ 30 mg/dL), an increased glucose infusion requirement to maintain normoglycaemia (>8 mg/ kg/min in neonate, >3 mg/kg/min in adults). Evidence of excessive or inadequate suppressed insulin secretion include detectable plasma insulin (≥ 1.25 μU/mL), and C-peptide (≥ 0.5 ng/mL), although these are less definitive than the evidence of excessive insulin action. Insulin concentration do not always correlate with biochemical evidence of insulin action; therefore, interpretation should be based primarily on the metabolic indicators of insulin action,rather than absolute insulin levels. A low or undetectable insulin level durin hypoglycemia does not exclude HI [2,3].

In neonates, evaluated before 72 hours of life, repeat testing after this period is recommended if hypoglycemia persists, to exclude transient neonatal hypoglycemia [2,3]. Infants with CHI are often large for gestational age and require high glucose infusion rates (>10 mg/kg/min), however, some may have normal birth weight, milder glucose requirements, and

present with hypoglycemia later in infancy [2,3].

Diffuse forms of CHI typically present with higher birth weights and greater glucose requirements, whereas, approximate half of those with focal form are large for gestational age [28]. Because of substantial clinical overlap, focal and diffuse forms cannot be reliably distinguished by clinical features alone.

Genetic testing is recommended when acquired causes are unlikely, particularly in diazoxide-unresponsive cases or in diazoxide-responsive cases persisting beyond three months. Identification of *ABCC8* and *KCNJ11* mutations is important for with diazoxide-unresponsive HI, as a paternally inherited mutations predicts focal forms with approximately 97% sensitivity [10]. Pancreatic imaging with ^{18}F-DOPA PET Scanning is useful for localizing potentially resectable focal lesions, although very small lesions may remain undetected, and a negative scan does not exclude focal disease [29].

TREATMENT

Despite efforts to maintain plasma glucose within taget range of 70–100 mg/dL, studies have shown that levels may fall below this threshold in up to 15%–20% of measurements in children with severe HI. In such cases, a lower glycemic target of approximately 63 mg/dL may be acceptable, depending on the frequency and severity of hypoglycemia and the availability of alternative therapeutic strategies [3]. Diazoxide remains the first-line pharmacological agent for the management of HH. However, patients with homozygous or compound heterozygous recessive mutations of *ABCC8* or *KCNJ11* causing diffuse CHI are typically unresponsive to diazoxide [10]. Octreotide, a somatostatin analogue, is used as a second-line agent, whereas lanreotide, glucagon, acarbose, sirolimus or everolimus may be considered in refractory cases. Surgical intervention is indicated when medical therapy fails [2,3]. Focal K_{ATP}-HI can be cured by limited resection, whereas diffuse CHI requires continued medical management, with near-total pancreatectomy reserved for severe, medically intractable cases. In large surgical cohorts, focal and diffuse types accounted for approximately 55% and 45% of cases, respectively [30]. Following near-total pancreatectomy, hypoglycemia recurs in up to 50%-60% of patients. Most achieve adequate glycemic control with adjunctive medical therapy, although a subset may require repeat surgery, Over time, nearly all patients eventually develop insulin-dependent diabetes [2,3].

CONCLUSION

Effective therapeutic options for CHI remain limited, and affected children continue to experience a high incidence of neurological sequelae due to hypoglycemia-induced brain injury. Improving long-term outcomes requires prompt recognition of hypoglycemia, accurate identification of underlying cause, timely initiation of appropriate treatment. Genetic diagnosis is essential for defining etiology, predicting phenotype, guiding targeted management.

AUTHOR CONTRIBUTIONS

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Exercise for Patients with Neuromuscular Diseases

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Neuromuscular diseases (NMDs) comprise a heterogeneous spectrum of inherited and acquired disorders affecting anterior horn cells, peripheral nerves, neuromuscular junctions, or skeletal muscle, resulting in progressive weakness, fatigue, and functional decline. Historically, exercise was discouraged due to concerns of "overuse weakness"; however, a growing body of evidence now supports the safety and efficacy of supervised submaximal exercise as a therapeutic intervention for various NMD subtypes. Moderate-intensity aerobic and strength training improves mitochondrial biogenesis, oxidative efficiency, and preserves neuromuscular integrity through activation of the AMPK–SIRT1–PGC-1α and mTORC1–Akt signaling pathways, while promoting antioxidant and anti-inflammatory responses. Individualized exercise programs tailored to the functional status of patients and adapted to the specific metabolic and structural characteristics of certain neuromuscular diseases improve endurance, muscle strength, and quality of life without accelerating disease progression. In the era of disease-modifying therapies, the role of exercise as a complementary measure to enhance therapeutic efficacy is gaining increasing scientific and clinical importance. A multimodal, individualized approach integrating aerobic exercise, strength training, flexibility training, respiratory training, and computer-assisted interventions under clinical supervision represents the current standard of care.

Key words: Neuromuscular disease, Therapeutic exercise, Aerobic training, Resistance training

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INTRODUCTION

Neuromuscular diseases (NMDs) represent a diverse group of inherited and acquired disorders affecting anterior horn cells, peripheral nerves, neuromuscular junctions, or skeletal muscle fibers. Despite their diverse etiologies, these disorders share common features, including progressive muscle weakness, fatigue, contractures, and loss of functional autonomy, which significantly impair quality of life and increase the burden of care. Historically, exercise was viewed with caution in this population. Since the mid-20th century, clinicians have warned of the risk of irreversible damage caused by voluntary muscle contraction, a notion termed "overuse weakness" [1,2]. Consequently, rest and immobility were often prescribed, which paradoxically exacerbated deconditioning, cardiorespiratory decline, and secondary complications such as contractures and osteoporosis.

A paradigm shift occurred in the late 20th century when controlled studies challenged this traditional view. Early research showed that supervised submaximal exercise could improve strength and endurance without accelerating disease progression [3,4]. Subsequent randomized controlled trials (RCTs) in various neuromuscular conditions, including Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), mitochondrial myopathies, and amyotrophic lateral sclerosis (ALS), have confirmed that appropriately dosed training is both safe and beneficial [5-7]. These results overturned previous dogma by establishing a crucial distinction between therapeutic activation and pathological overuse. The principle of "training without exhaustion" has now become a central tenet of

modern neuromuscular rehabilitation.

At the molecular level, exercise activates adaptive pathways that improve cellular resilience. Aerobic activity upregulates the AMPK–PGC-1α axis, promoting mitochondrial biogenesis, oxidative phosphorylation, and fatigue resistance [8-10]. Moderate resistance training stimulates mTORC1-mediated protein synthesis, facilitating myofibrillar repair without oxidative injury [11]. Furthermore, exercise modulates inflammation and redox homeostasis by reducing pro-inflammatory cytokines (TNF-α, IL-6) and increasing the expression of antioxidant enzymes [12]. These findings redefine exercise as a biologically active therapy that can shift muscle metabolism from a catabolic to an anabolic balance.

Despite the growing body of evidence, implementation in clinical practice remains inconsistent. Variations in study design, training intensity, and safety monitoring have led to heterogeneous results, leaving clinicians uncertain about optimal prescriptions. Therefore, this review aims to synthesize current evidence on the role of exercise in neuromuscular diseases, presenting disease-specific recommendations from clinical studies, the efficacy and safety of key exercise modalities, and the prospects for integrating digital health and precision rehabilitation into clinical care.

DISEASE-SPECIFIC EXERCISE RECOMMENDATIONS

Neuromuscular diseases differ in pathophysiology, disease trajectory, and residual motor potential; thus, exercise prescription must be individualized. A growing body of RCTs and cohort studies demonstrates that carefully done, submaximal programs improve performance and quality of life without accelerating muscle degeneration.

Amyotrophic lateral sclerosis

In ALS, progressive degeneration of motor neurons leads to general weakness and difficulty breathing. Moderate-intensity aerobic and resistance training (40%–60% of VO_2max; rating of perceived exertion [RPE] ≤ 13) has been shown to improve motor performance and attenuate the rate of functional decline [13,14]. Dal Bello-Haas et al. [13] showed significant improvements in Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) scores after a 12-week combined training program. Exercise intensity exceeding 70% of the individual's maximum heart rate (HRmax) or the presence of post-exercise muscle soreness persisting for more than 24 hours should be considered an indicator for temporary exercise cessation. Periodic assessment of serum creatine kinase (CK) levels and forced vital capacity (FVC) is recommended to monitor for subclinical muscle injury and evolving respiratory compromise.

Duchenne muscular dystrophy

Dystrophin deficiency increases the susceptibility of muscle fibers to eccentric loading. Accordingly, safe exercise modalities for patients with DMD include gentle concentric or aquatic activities performed at intensities ≤ 40% of VO_2max, two to three times per week [15,16]. Aquatic therapy has been shown to improve endurance and postural control without increasing serum CK levels. However, eccentric exercises and high-resistance training are contraindicated due to the risk of muscle fiber damage.

Spinal muscular atrophy

Residual motor neurons retain the capacity for compensatory hypertrophy in response to low-load progressive resistance training [17]. Abresch et al. [18] reported improvements in posture and respiratory function after 8–12 weeks of training with ≤ 50% of the one-repetition maximum (1RM) combined with daily inspiratory muscle training. Training programs should include careful monitoring of fatigue and appropriate respiratory support to ensure safety and optimize functional outcomes.

With the advent of disease-modifying therapies such as *nusinersen*, *onasemnogene abeparvovec*, and *risdiplam*, rehabilitation and exercise interventions have gained importance as complementary strategies to optimize functional recovery and maintain motor performance in patients with SMA [19].

Mitochondrial myopathies

Aerobic deficits are prominent in patients with mitochondrial myopathies; therefore, structured aerobic exercise may enhance oxidative enzyme activity and attenuate lactate accumulation [10,20]. Tarnopolsky and Halonen demonstrated significant improvements in peak VO_2 after submaximal cycling performed at 50%–70% of VO_2max for 20–30 minutes per session. High-intensity interval training should be avoided to reduce the risk of metabolic crises.

Inflammatory myopathies

During phases of inactivity or remission, low-load circuit or flexibility training may improve endurance and quality of life

without increasing serum CK levels [21,22]. In case of active inflammation or feverish illness, training should be discontinued. Regular CK monitoring and medical supervision remain essential to ensure safety and prevent worsening of disease activity.

Slowly progressive NMDs

Combined aerobic-strength training protocols have demonstrated synergistic benefits in patients with slowly progressive neuromuscular disorders. Programs incorporating submaximal cycling at approximately 60% of HRmax for 12 weeks have demonstrated an increase in aerobic capacity of approximately 15% and maintenance of performance in activities of daily living (ADL) and fatigue tolerance, particularly in cases of myotonic dystrophy or facioscapulohumeral muscular dystrophy [23-25]. The integration of moderate resistance exercises, targeting major proximal and antigravity muscle groups, further promotes muscular endurance and functional stability without inducing myofibrillar damage or excessive elevations in serum CK.

EXERCISE MODALITIES AND IMPLEMENTATION STRATEGIES

The clinical effectiveness of exercise in NMDs is determined not only by the total workload but also by the type, intensity, and context of the intervention. Each exercise modality engages distinct but interdependent physiological systems—metabolic, neuromuscular, cardiopulmonary, and neuroplastic—that collectively contribute to adaptive remodeling and functional resilience. Therefore, a multimodal exercise model integrating aerobic, strength, flexibility, breathing, and task-oriented functional training, with or without digital monitoring and feedback, is considered the optimal therapeutic approach.

Aerobic training

Aerobic exercise remains the cornerstone of metabolic conditioning in patients with neurodegenerative diseases. Through activation of the AMPK–SIRT1–PGC-1α signaling cascade, it enhances mitochondrial biogenesis, upregulates oxidative enzyme activity, and optimizes substrate utilization, thereby increasing cellular energy metabolism and fatigue resistance [8,9]. The physiological benefits of aerobic exercise include increased endurance, reduced lactate accumulation, and improved resistance to fatigue.

Clinical trials in patients with mitochondrial myopathies, ALS, and muscular dystrophies have demonstrated significant improvements in VO_2 max, six-minute walk distance, and perceived exertion after 8 to 12 weeks of moderate-intensity training (40%–70% of VO_2max; RPE≤13; 20–30 minutes per session, two to four times per week) [7,17,20]. Regular monitoring of heart rate and serum CK levels is essential to ensure safety and prevent overexertion. For individuals with joint or respiratory limitations, supervised aquatic exercise or cycle ergometers are safe and effective alternatives for maintaining aerobic capacity.

Resistance training

Resistance training promotes muscular strength and endurance primarily through activation of the mTORC1 and IGF-1–Akt signaling pathways, while simultaneously suppressing catabolic processes [3,26]. Low- to moderate-intensity loading (≤50% of 1RM, 10–15 repetitions, two to three sessions per week) has been shown to preserve myofibrillar integrity and prevent sarcolemmal rupture. High-resistance eccentric exercises should be avoided, and alternating rest intervals are recommended to minimize the risk of overuse injury and delayed recovery [13].

Flexibility and stretching training

Flexibility exercises play an important role in the prevention of joint contractures, spasticity, and postural deformities by maintaining soft tissue extensibility, joint mobility, and optimal flexibility of muscles and tendons [27]. Regular stretching also improves blood flow to the periarticular tissue and promotes proprioceptive feedback, contributing to greater comfort and less pain. A daily practice of gentle, sustained stretching—usually 10 to 30 seconds per muscle group, repeated two to three times—is recommended to maintain range of motion and relieve stiffness [28].

Excessive stretching should be avoided, especially in cases of active inflammation or fibrotic progression, as excessive tension can exacerbate microtrauma and inflammatory reactions. Wearing orthoses or positioning aids can promote correct joint alignment and prevent the development of contractures in patients with severe muscle weakness or impaired voluntary control. When performed regularly under clinical supervision, flexibility training is an essential component of comprehensive neuromuscular rehabilitation, complementing aerobic and resistance exercises to maintain functional mobility and comfort.

Respiratory muscle training

Respiratory muscle training, particularly with a focus on strengthening the inspiratory muscles, is an important complementary measure for maintaining ventilation function and airway clearance in patients with neuromuscular diseases [29,30]. Targeted training of the inspiratory muscles improves diaphragmatic contractility, promotes chest expansion, and increases cough efficiency, thereby limiting the progression of hypoventilation and recurrent respiratory infections. Daily inspiratory muscle training with a threshold load (approximately 15 to 20 minutes per day) has been shown to improve inspiratory muscle strength (e.g., maximum inspiratory pressure [MIP]) and cough efficiency, and may help stabilize or modestly improve lung function in certain patient cohorts [30]. Evidence suggesting that this intervention delays ventilator dependence remains preliminary, particularly in ALS and DMD [31-33].

Aquatic therapy

Aquatic therapy provides a supportive, low-impact environment that facilitates movement for patients with NMDs. The buoyancy of the water counteracts gravity, reducing the mechanical load on weight-bearing joints and allowing patients with muscle weakness or pain to perform functional movements with less effort and discomfort. At the same time, hydrostatic pressure improves venous return, reduces peripheral edema and promotes proprioceptive signals, contributing to better postural control and overall cardiovascular performance.

Therapeutic sessions in thermoneutral water (approximately 30–32°C) promote muscle relaxation, reduce spasticity, and enable smooth, coordinated movements. Regular hydrotherapy has been proven to improve endurance, flexibility, and subjective well-being through its combined effects on circulation, neuromuscular activation, and psychological relaxation [15,16].

Hind et al. [34] reported significant improvements in balance, walking stability, and aerobic capacity in children with DMD following a structured aquatic exercise program. These findings underscore the benefit of aquatic environments for maintaining function in children with progressive muscle weakness.

Therapist supervision is essential to ensure proper technique, intensity control, and safety, particularly in individuals with respiratory difficulties or those prone to fatigue. Exercise intensity should be increased gradually, with an emphasis on continuous rather than ballistic movements. Perceived exertion, heart rate, and post-session fatigue should be carefully monitored. The integration of buoyancy aids and shallow-water equipment allows for greater treatment personalization and expands opportunities for safe participation, regardless of disease stage.

Table 1 provides an overview of the main exercise modalities used in the rehabilitation of NMDs, describing their underlying physiological rationale and key clinical considerations for safe and effective implementation.

Each modality offers distinct physiological benefits: aerobic and strength training improve endurance and strength; stretch-

Table 1. Summary of exercise modalities, physiological rationale, and clinical considerations in the rehabilitation of neuromuscular diseases

Exercise Modality	Physiological rationale/ primary mechanism	Recommended parameters	Clinical considerations
Aerobic Training	Enhances mitochondrial biogenesis via AMPK–SIRT1–PGC-1α axis; increases oxidative enzyme activity and fatigue resistance	40%–70% VO_2max, RPE≤13, 20–30 min/session, 2–4×/week	Monitor HR & CK; avoid >70% HRmax; aquatic or cycling modes for joint/respiratory limitation
Resistance Training	Activates mTORC1–IGF-1–Akt pathway; improves muscle protein synthesis and strength	≤50% 1RM, 10–15 reps, 2–3×/week	Alternate-day sessions; avoid high-resistance eccentric work; combined with stretching
Flexibility/Stretching	Maintains joint mobility and muscle-tendon compliance; reduces contracture, spasticity	Gentle static stretch 10–30 sec, 2–3 reps/muscle, daily	Avoid overstretching during inflammation/fibrosis; use orthotics for positioning
Respiratory Muscle Training (IMT)	Strengthens diaphragm and accessory inspiratory muscles; activates AMPK–PGC-1α to improve endurance	30%–60% MIP, 15–20 min/day, 5–7 days/week	Monitor SpO_2 & symptoms; discontinue if desaturation <90% or severe fatigue; combine with NIV or MI-E if needed
Aquatic/ Hydrotherapy	Buoyancy & hydrostatic pressure reduce mechanical load, enhance proprioception and venous return	30–32 °C water, 20–40 min/session, 2–3×/week	Supervised sessions; gradual intensity progression; caution in severe respiratory or cardiac dysfunction

VO_2max, maximal oxygen uptake; RPE, rating of perceived exertion; HR, heart rate; HRmax, maximal heart rate; CK, creatine kinase; 1RM, one-repetition maximum; MIP, maximal inspiratory pressure; SpO_2, peripheral oxygen saturation; NIV, non-invasive ventilation; MI-E, mechanical insufflation-exsufflation.

ing preserves joint range of motion; and respiratory and aquatic therapy promotes cardiopulmonary and postural health. Combined multimodal programs provide maximum benefit in individualized, supervised programs.

CONCLUSION

Physical exercise was once contraindicated but is now an essential, evidence-based therapeutic modality in the treatment of NMDs. A growing body of research demonstrates that submaximal exercise prescription, carefully individualized based on disease progression and each patient's functional status, results in clinically meaningful improvements in endurance, metabolic efficiency, and psychosocial well-being, without accelerating muscle degeneration.

Individualized exercise prescription is therefore fundamental to the rehabilitation of NMDs. Given the heterogeneity of disease trajectories and residual motor capacity, aerobic, strength, flexibility, and respiratory training must be tailored in terms of frequency, intensity, and modalities. Such patient-specific programming maximizes therapeutic efficacy while minimizing the risks of overwork weakness and fatigue.

In summary, physical exercise is now recognized as a cornerstone of comprehensive neuromuscular rehabilitation and no longer as a complementary intervention. When delivered at submaximal intensity, guided by physiological monitoring, and supervised by skilled clinicians, it enhances motor performance, delays functional decline, and improves quality of life. Future directions should emphasize the harmonization of international guidelines, establishment of standardized safety and intensity parameters, and validation of digital biomarkers to realize precision, adaptive rehabilitation across the spectrum of neuromuscular diseases.

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Comprehensive Characterization of *KMT2D* Variants in Korean Patients with Kabuki Syndrome: Expanding the Clinical and Genetic Landscape

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Background: Kabuki syndrome (KS) is a rare disorder characterized by distinctive craniofacial features, developmental delay, short stature, and involvement of multiple organ systems. The genotype–phenotype correlation in KS remains incompletely understood.
Methods: This study aimed to delineate the clinical and genetic spectrum of KS in a cohort of 27 Korean patients. Twenty-seven individuals clinically suspected of KS were evaluated at Pusan National University Children's Hospital between March 2009 and November 2022. Comprehensive assessments were conducted across multiple systems. Statistical comparisons were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables (IBM SPSS Statistics v21).
Results: The mean age at diagnosis was 6.90±6.71 years, with an average diagnostic delay of 4.56±5.03 years. All patients exhibited characteristic facial features of KS. Developmental delay was observed in 92.6% of cases, followed by short stature, skeletal and ENT abnormalities (63.0% each), congenital heart disease (59.3%), ophthalmologic issues (51.9%), neurologic and urogenital involvement (48.1% each), immune dysfunction (18.5%), and hematologic malignancy (3.7%). Pathogenic or likely pathogenic *KMT2D* variants were identified in 23 patients (85.2%), while 4 remained genetically undiagnosed. Among the detected variants, 8 were nonsense, 7 frameshift, 6 missense, 1 splicing, and 1 duplication variant; notably, 18 (78.3%) of these were novel. Patients with pathogenic *KMT2D* variants were diagnosed at a significantly younger age compared to variant-negative patients ($P=0.05$). Those harboring truncating variants exhibited a higher burden of multi-organ involvement compared to individuals with non-truncating variants (4.9±1.4 vs. 3.0±2.3; $P=0.016$).
Conclusion: This study broadens the clinical and molecular landscape of Kabuki syndrome in Korean patients.

Key words: Kabuki syndrome, Characterization, Variants, Phenotype

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INTRODUCTION

Kabuki syndrome (KS; OMIM #147920 [KS1], #300867 [KS2]) is a congenital disorder characterized by distinctive craniofacial dysmorphism—such as long palpebral fissures with eversion of the lateral third of the lower eyelid, large or cupped ears—along with multiple congenital anomalies, short stature, and intellectual disability [1-3]. KS has been documented across diverse ethnic groups, including Northern European, Italian, Brazilian, Vietnamese, Indian, Arabic, Chinese, Japanese, Mexican, and African populations [4,5]. The estimated prevalence ranges from 1 in 32,000 to 1 in 86,000 individuals [6,7]. In 2010, *KMT2D* was identified as the primary causative gene, accounting for over 80% of cases [6-9]. Located on chromosome 12q13.12, *KMT2D* comprises 54 exons and plays a critical role in regulating the transcription of genes involved in embryonic development [8].

In 2012, *KDM6A* (lysine demethylase 6A; also known as *UTX*, NM_021140.2) was identified as a second causative gene, responsible for approximately 6% to 10% of cases [10,11]. This gene is located on chromosome Xp11.3 and consists of 29 exons; it modulates gene expression in cooperation with *KMT2D* [6,8]. To date, more than 816 unique *KMT2D* variants associated with KS have been reported, including deletions, insertions, point mutations, and splice-site alterations (Human Gene Mutation Database [HGMD], release 2023.1; http://www.hgmd.org/).

In Korea, a 2014 review identified 12 reported cases of KS [8] with subsequent literature limited to isolated case reports. The present study aims to expand the clinical and molecular understanding of KS by characterizing 27 Korean patients and contributing newly identified *KMT2D* variants to the existing mutational spectrum.

METHODS

Subjects and clinical evaluation

This study included 27 patients diagnosed with KS, all of whom were assessed at Pusan National University Children's Hospital in Yangsan, South Korea, between March 2009 and November 2022. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Comprehensive clinical data were collected for each participant, including age, sex, phenotypic spectrum across multiple systems (cardiologic, endocrinologic, gastrointestinal, hemato-oncologic, neurologic, musculoskeletal, ophthalmologic, otolaryngologic, urogenital, and immune systems), response to growth hormone therapy, and underlying genetic alterations.

Diagnosis of KS was based on established criteria [12], which include a history of infantile hypotonia and developmental delay and/or intellectual disability, in addition to at least one of the following major features:

(1) A confirmed pathogenic or likely pathogenic variant in either *KMT2D* or *KDM6A*, and

(2) Characteristic craniofacial dysmorphisms such as elongated palpebral fissures (≥2 SD above the age-specific mean) with eversion of the lateral lower eyelid, accompanied by at least two of the following:

(a) Arched and broad eyebrows with lateral thinning or notching,

(b) Short columella with a depressed nasal tip,

(c) Large, prominent, or cupped ears, and

(d) Persistent fetal fingertip pads.

Involvement of major organ systems was defined by clinical manifestations affecting the cardiovascular, neurological, respiratory, gastrointestinal, or renal systems.

Genetic analysis

Genetic testing was performed following informed consent from all participants or their legal guardians. Genomic DNA was extracted from peripheral blood leukocytes using the Puregene DNA Isolation Kit (Gentra, Minneapolis, MN, USA).

Initial genetic analysis included targeted amplification of the coding regions of *KMT2D* and *KDM6A* using polymerase chain reaction (PCR) with gene-specific primers, followed by direct sequencing on an ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

For broader molecular profiling, targeted exome sequencing was conducted using the TruSight One Sequencing Panel (Illumina, San Diego, CA, USA) and mapped to the UCSC human genome reference (hg19). In selected cases, whole exome sequencing (WES) was performed using the NovaSeq6000 platform (Illumina, San Diego, CA, USA) with 150 bp paired-end reads. Exonic regions of approximately 22,000 human genes were enriched using one of the following capture kits, depending on the enrollment period: Agilent SureSelect (version C2, December 2018), Twist Bioscience Capture Kit (San Francisco, CA, USA), or xGen Exome Research Panel v2 (Integrated DNA Technologies, Coralville, IA, USA).

Variants were classified and interpreted in accordance with the standards and guidelines established by the American College of Medical Genetics and Genomics (ACMG).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). Continuous variables were analyzed using the Wilcoxon rank sum test (Mann–Whitney U test), and categorical variables were evaluated using Fisher's exact test. A P-value < 0.05 was considered indicative of statistical significance.

RESULTS

Clinical characteristics of 27 patients with Kabuki syndrome

The clinical profiles of 27 patients with genetically or clinically diagnosed KS are summarized in Table 1. The cohort comprised 14 males and 13 females. The mean gestational age at birth was 38+0 weeks, and the average birth weight was 2.80 ± 0.71 kg (range: 1.50–4.18 kg). Premature birth was observed in 6 patients (22.2%). The mean age at diagnosis was 6.90 ± 6.71 years (range: 0.16–27.18 years). The first clinical symptom appeared at a mean age of 2.34 ± 5.68 years (range: 0.00–26.89 years), with an average diagnostic delay of 4.56 ± 5.03 years (range: 0.12–15.39 years). Developmental delay or intellectual disability (ID) was the most common initial presentation (n = 6), followed by congenital heart disease (n = 5), prenatal ultrasound abnormalities (n = 4), facial dysmorphism (n = 3), seizures (n = 2), and isolated findings such as abnor-

Table 1. Baseline demographic characteristics and comprehensive clinical and genetic profiles of patients with Kabuki syndrome (n=27)

Pt	Age at Dx (yr)	Sex	Short stature	ID/DD	Sz	CHD	Uro-genital problem	CPP	Oph lesions	OTL problem	HO abnor-mality	OBGY problem	Skeletal deformity	Immune dysfuc-tion	Brain MR ab-normality	Gene	NT change	AA change	C	Novelty	Method
K01	1.82	M	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	Y	*KMT2D*	c.16501C>T	p.R5501*	P	reported	Sing
K02	7.62	F	N	Y	N	N	N	N	Y	N	N	N	Y	N	NA	*KMT2D*	c.13259G>A	p.R4420Q	VUS	novel	Sing
K03	14.02	F	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	NA	*KMT2D*	c.2579delT	p.L860Rfs*70	P	novel	TES
K04	13.04	M	Y	Y	N	Y	N	N	N	Y	N	N	Y	Y	NA	*KMT2D*	c.15670C>T	p.R5224C	LP	novel	Sing
K05	0.40	M	Y	Y	N	Y	N	N	Y	N	N	N	N	N	NA	*KMT2D*	c.5779C>T	p.Q1927*	LP	novel	TES
K06	0.16	M	Y	Y	N	Y	Y	N	N	Y	N	N	N	Y	NA	*KMT2D*	c.12084delC	p.V4029*	LP	novel	TES
K07	6.36	F	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	N	*KMT2D*	c.8107G>T	p.E2703*	P	novel	Sing
K08	13.79	F	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	N	N	*KMT2D*	c.1506C>T	p.R5021*	P	novel	WES
K09	15.57	M	N	Y	Y	N	N	N	N	N	N	N	N	N	Y	*KMT2D*	c.13732C>A	p.P4578T	VUS	novel	Sing
K10	0.31	F	Y	Y	N	Y	Y	N	Y	Y	N	N	Y	N	NA	*KMT2D*	c.6827dupC	p.P2277Tfs*22	P	novel	TES
K11	4.05	M	N	Y	N	N	N	N	N	Y	N	N	N	N	NA	*KMT2D*	c.16519G>A	p.E5507K	VUS	novel	TES
K12	1.38	M	Y	Y	N	N	N	N	Y	Y	N	N	N	N	NA	*KMT2D*	c.14945G>A	p.W4982*	LP	novel	TES
K13	12.62	F	N	Y	N	N	Y	N	Y	Y	N	N	Y	N	NA	*KMT2D*	c.3906+2T>C	splicing	P	reported	TES
K14	15.43	M	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	*KMT2D*	c.10750C>T	p.Q3584T	LP	novel	WGS
K15	0.38	M	N	N	N	Y	Y	N	N	Y	N	N	N	N	NA	*KMT2D*	c.7613dupT	p.Q2540Sfs*115	LP	reported	Pan
K16	2.81	F	Y	Y	N	Y	Y	Y	N	Y	N	N	Y	N	Y	*KMT2D*	c.6595delT	p.Y2199Ifs*65	P	reported	TES
K17	3.07	M	N	Y	N	N	N	N	NA	NA	N	N	N	N	NA	*KMT2D*	c.10151_10171dup	p.T3384_C3390dup	VUS	novel	WES
K18	0.55	F	Y	Y	N	Y	Y	N	N	N	N	N	Y	N	N	*KMT2D*	c.2819C>A	p.S940*	P	novel	WES
K19	3.16	M	N	Y	N	N	Y	N	N	N	N	N	Y	N	NA	*KMT2D*	c.9961C>T	p.R3321*	LP	reported	Pan
K20	4.05	M	Y	Y	N	Y	N	N	Y	N	N	N	Y	Y	NA	*KMT2D*	c.4271G>T	p.C1424F	P	novel	WES
K21	7.13	F	Y	Y	Y	Y	Y	NA	Y	Y	N	N	Y	N	N	*KMT2D*	c.14404delG	p.A4802Qfs*6	P	novel	Sing
K22	2.42	F	Y	Y	Y	Y	Y	N	NA	Y	N	N	Y	N	N	*KMT2D*	c.6553del	p.L2185Wfs*79	P	novel	Sing
K23	0.96	M	N	Y	N	N	N	N	NA	Y	N	N	N	N	NA	*KMT2D*	c.12835dup	p.A4279Gfs*55	LP	novel	Sing
K24	14.27	F	Y	N	N	N	N	N	NA	NA	N	N	Y	N	NA	*ND*	ND	ND	NA	NA	WES
K25	7.62	F	N	Y	Y	N	N	N	N	N	N	N	N	N	NA	*ND*	ND	ND	NA	NA	WES
K26	27.18	F	Y	Y	N	Y	N	N	Y	N	N	N	N	N	N	*ND*	ND	ND	NA	NA	WES
K27	6.23	M	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	NA	*ND*	ND	ND	NA	NA	WGS

Pt, patients; Dx, diagnosis; yr, years old; ID, intellectual disability; DD, developmental delay; Sz, seizure; CHD, congenital heart disease; CPP, central precocious puberty; Oph, ophthalmologic; OTL, otolaryngological; HO, hemato-oncological; OBGY, obstetric & gynecological; NT, nucleotide; AA, aminoacid; C, classification; M, male; F, female; Y, yes; N, no; NA, not applicable; P, pathogenic; LP, likely pathogenic; VUS, variants of uncertain significance; ND, not determined; Sing, single gene analysis; TES, targeted exome sequencing; WES, whole exome sequencing; WGS, whole genome sequencing; Pan, Panel sequencing.

mal hearing test, feeding intolerance, and short stature (each n=1). All patients exhibited typical craniofacial features characteristic of KS, such as long palpebral fissures with eversion of the lateral third of the lower eyelid and/or prominent ears. A majority of patients (92.6%, 25/27) demonstrated global developmental delay or ID. Short stature (height below −2 SD) was identified in 17 patients (63.0%), and 17 patients (63.0%) also exhibited musculoskeletal anomalies including scoliosis or kyphosis (n=13), hip dislocation (n=2), recurrent patellar dislocation (n=1), and cleidocranial dysostosis (n=1). Otolaryngologic manifestations were seen in 17 patients (63.0%), primarily otitis media (n=14) and sensorineural hearing loss (n=8), with less frequent findings of subglottic stenosis (n=1) and obstructive sleep apnea (n=1). Congenital heart disease was present in 16 patients (59.3%), including atrial septal defect (56.3%), ventricular septal defect (43.8%), patent ductus arteriosus (37.5%), and other less common anomalies such as coarctation of the aorta, aortic valve stenosis, and complex congenital heart defects (e.g., hypoplastic left heart syndrome, double outlet right ventricle). Ophthalmologic abnormalities were observed in 14 patients (51.9%), with strabismus being the most prevalent (n=8), followed by ectropion, entropion, and other structural anomalies. Neurological manifestations were present in 13 patients (48.1%), with seizures being the most frequent (n=8). Among those with seizures, electroencephalogram (EEG) findings varied: normal (n=3), focal epilepsy (n=3), and diffuse cerebral dysfunction (n=1). Urogenital anomalies were identified in 13 patients (48.1%), including structural anomalies such as horseshoe kidney (n=5), unilateral renal hypoplasia (n=3), and renal duplication or agenesis. Genital abnormalities included cryptorchidism (n=2), micropenis (n=1), and uterine malformations (n=2). Cleft palate was present in 10 patients (37.0%), and failure to thrive was documented in 9 patients (33.3%). Dental anomalies (n=7, 25.9%) and thyroid disorders (n=6, 22.2%; including both congenital hypothyroidism and Hashimoto's thyroiditis) were also noted. Immunologic abnormalities were reported in 5 patients (18.5%), consisting of T-cell subset deficiencies and hypogammaglobulinemia. One patient developed both stage IV Burkitt's lymphoma and a mature teratoma of the testis.

Efficacy of recombinant human growth hormone (rhGH) therapy

Among 17 patients with short stature, four prepubertal individuals underwent rhGH therapy. Two patients had confirmed growth hormone deficiency via provocation testing. One of these showed a height velocity of 6.0 cm/year after treatment, whereas the other could not be followed long enough for response evaluation. Two additional patients without confirmed GH deficiency also demonstrated favorable responses to rhGH, with annual height velocities of 8.5 cm (height SDS from -2.63 to -2.11) and 8.2 cm (height SDS from -3.55 to -2.69), respectively. The mean height SDS at last follow-up across all treated patients was −1.77 ± 1.51.

Genetic findings in 27 patients with KS

Genetic analysis revealed pathogenic or likely pathogenic variants in *KMT2D* in 23 of 27 patients (85.2%). No causative variants in either *KMT2D* or *KDM6A* were identified in the remaining four patients, two of whom underwent whole genome sequencing (WGS) without revealing additional findings (Fig. 1). Among the *KMT2D* variants, there were 8 nonsense, 7 frameshift, 6 missense, 1 duplication, and 1 splicing variant. Notably, 18 out of 23 variants (78.3%) were novel and absent

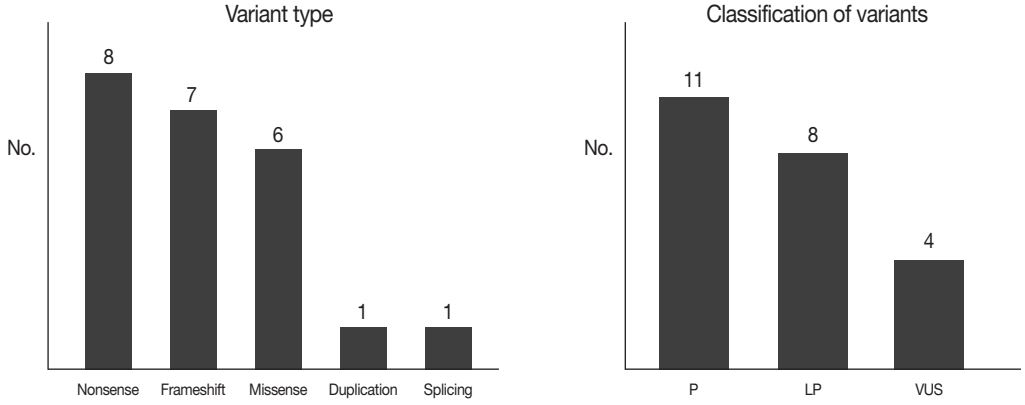


Fig. 1. Genetic profiles of Kabuki syndrome based on variant classification. P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance.

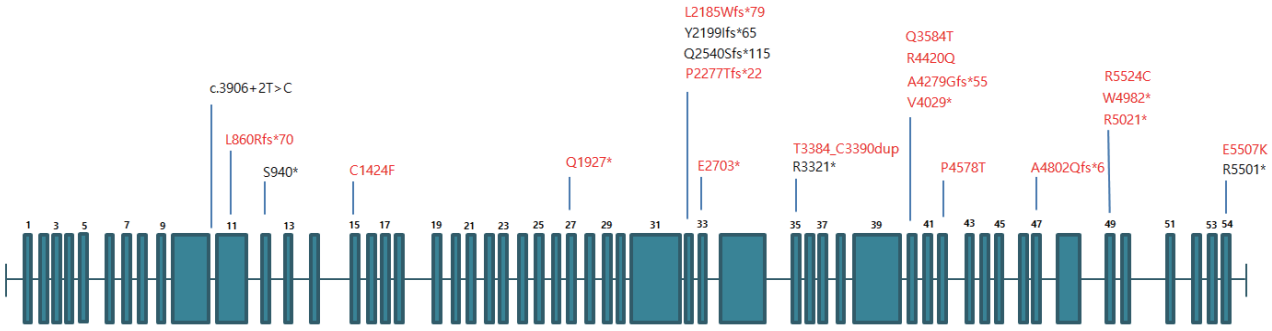


Fig. 2. Detailed mapping of *KMT2D* variants in Kabuki syndrome: Variant type distribution across all 54 exons, with novel variants denoted in red.

Table 2. Comparative analysis of clinical phenotypes between genetically confirmed and genetically unresolved cases of Kabuki syndrome

	Variant-positive KS n=23 (85.2%)		Variant-negative KS n=4 (14.8%)		*P*-value *
Sex (no., %)	M	F	M	F	
	13 (56.5%)	10 (43.5%)	1 (25.0%)	3 (75.0%)	
Age of first symptom onset (yr)					0.122
Median (IQR)	0.03 (1.11)		7.87 (22.23)		
Age at diagnosis (yr)					0.050
Mean±SD	5.70±5.52		13.82±9.56		
Median (range)	3.16 (0.16-15.57)		10.94 (6.23-27.18)		
Current age (yr)					0.147
Mean±SD	9.84±6.05		17.51±9.23		
Median (range)	8.31 (1.28-20.18)		14.34 (10.82-30.54)		
Facial dysmorphism (no., %)	23 (100)		4 (100)		>0.99
Global developmental delay or intellectual disability (no., %)	22 (95.7)		3 (75.0)		0.279
Otolaryngological disorder (no., %)	16 (69.6)		1 (25.0)		0.128
Orthopedic disorder (no., %)	15 (65.2)		2 (50.0)		0.613
Congenital heart disease (no., %)	14 (60.9)		2 (50.0)		0.767
Urogenital disorder (no., %)	12 (52.2)		1 (25.0)		0.325
Short stature (no., %)	14 (60.9)		3 (75.0)		0.576
Ophthalmologic problem (no., %)	12 (52.2)		2 (50.0)		0.937
Cleft palate (no., %)	9 (39.1)		1 (25.0)		>0.99
Feeding intolerance (no., %)	8 (34.8)		0		0.285
Failure to thrive (no., %)	8 (34.8)		1 (25.0)		>0.99
Neurologic problems (no., %)	10 (43.5)		3 (75.0)		0.253
Dental problem (no., %)	7 (30.4)		0		0.545
Seizure (no., %)	6 (26.1)		2 (50.0)		0.489
Immunologic abnormality (no., %)	5 (21.7)		0		0.561
Congenital hyperinsulinemic hypoglycemia (no., %)	3 (13.0)		0		>0.99
Carnitine deficiency (no., %)	1 (4.3)		0		>0.99
Attention deficit hyperactive disorder (no., %)	2 (8.7)		0		>0.99
Malignancy (no., %)	1 (4.3)		0		>0.99
Thyroid disease (no., %)	5 (21.7)		1 (25.0)		>0.99
Central precocious puberty (no., %)	2 (8.7)		0		>0.99
Diabetes mellitus (no., %)	1 (4.3)		0		>0.99
Growth hormone deficiency (no., %)	1 (4.3)		1 (25.0)		0.153

no., numbers; yr, years old; IQR, interquartile range; SD, standard deviation. *Mann-Whitney U test.

from public databases such as ESP6500, 1000 Genomes, dbSNP137, and KPGP. According to ACMG guidelines, variants were classified as pathogenic (n = 11), likely pathogenic (n = 8), or of uncertain significance (n = 4). Each patient harbored a unique, non-recurrent mutation. The variants were widely distributed throughout exons 1 to 54 of *KMT2D*, although clustering was observed in exons 32, 40, and 49 (Fig. 2).

Clinical comparison between variant-positive and variant-negative Patients

Comparison between variant-positive (n = 23) and variant-negative (n = 4) patients revealed a statistically significant younger age at diagnosis in the variant-positive group ($P = 0.05$) (Table 2).

Clinical comparison between truncating and non-truncating variant groups

When comparing patients with truncating variants (nonsense and frameshift) and those with non-truncating variants (missense, splicing, duplication), the truncating variant group exhibited a significantly higher burden of major organ involvement (mean 4.9 ± 1.4 vs. 3.0 ± 2.3, $P = 0.016$) (Table 3).

Clinical comparison between mutational hotspot and non-hotspot groups

Patients with mutations located in identified *KMT2D* hotspot exons (32, 40, 49) were compared with those harboring mutations outside these regions. No statistically significant differences in clinical manifestations were observed between the two groups (Supplementary Table 1).

DISCUSSION

In this study, we comprehensively analyzed the clinical and genetic features of 27 patients with KS in Korea. As a syndrome characterized by distinct craniofacial dysmorphisms, early recognition based on clinical suspicion remains crucial for timely diagnosis. This is underscored by our high diagnostic yield (85.2%) for pathogenic variants in *KMT2D*, which reflects both the recognizability of the syndrome and the importance of clinician awareness [13].

Global developmental delay or intellectual disability was observed in 92.6% of our cohort, consistent with previous reports [6]. Developmental delay in KS is multifactorial and may result from cognitive dysfunction, hypotonia, skeletal anomalies, cardiac defects, gastrointestinal complications, and hearing impairment [6]. In addition, short stature, musculoskeletal abnormalities, otolaryngologic disorders, congenital heart disease (CHD), and ophthalmologic anomalies were all present in more than half of the patients (63.0%, 63.0%, 63.0%, 59.3%, and 51.9%, respectively), highlighting the multisystemic nature of KS (Fig. 3).

CHD are among the most commonly reported systemic findings in KS, with prevalence varying across studies but generally estimated at around 70% [6,7]. In our cohort, CHD was identified in 59.3% of patients. This is consistent with the known role of *KMT2D* in murine cardiogenesis [14,15]. Consistent with previous literature, left-sided lesions such as atrial septal defect, ventricular septal defect, and coarctation of the aorta were predominant [5–7,13,14]. Interestingly, one patient (K20) harboring a novel *KMT2D* variant (c.4271G>T) exhibited scimitar syndrome, a rare vascular anomaly seldom reported in KS [5,8,16]. This patient also had T-cell dysfunction, characteristic facial features, and was later diagnosed with partial growth hormone (GH) deficiency, illustrating the complex interplay between genotype and multisystem involvement.

Short stature, reported in up to 70% of KS patients [6,14], was observed in 63.0% of our cohort. Emerging evidence sug-

Table 3. Clinical characterization of Kabuki syndrome according to truncating versus non-truncating *KMT2D* mutations

	Truncating variant group (N = 15)	Non-truncating variant group (N = 8)	*P*-value
Major organ involvements (mean ± SD)	4.9 ± 1.4	3.0 ± 2.3	0.016*
Congenital heart defects (no., %)	11 (73.3)	3 (37.5)	0.179†
Global developmental delay or intellectual disability (no., %)	14 (93.3)	8 (100)	>0.99†
Seizure (no., %)	4 (26.7)	2 (25.0)	>0.99†
Immune dysfunction (no., %)	2 (13.3)	3 (37.5)	0.297†
Short stature (no., %)	11 (73.3)	3 (37.5)	0.179†
Ophthalmologic lesion (no., %)	8 (53.3)	4 (50.0)	>0.99†
Urogenital anomaly (no., %)	10 (66.7)	2 (25.0)	0.089†

no., numbers; SD, standard deviation. *Mann-Whitney U test; †Fisher's exact test.

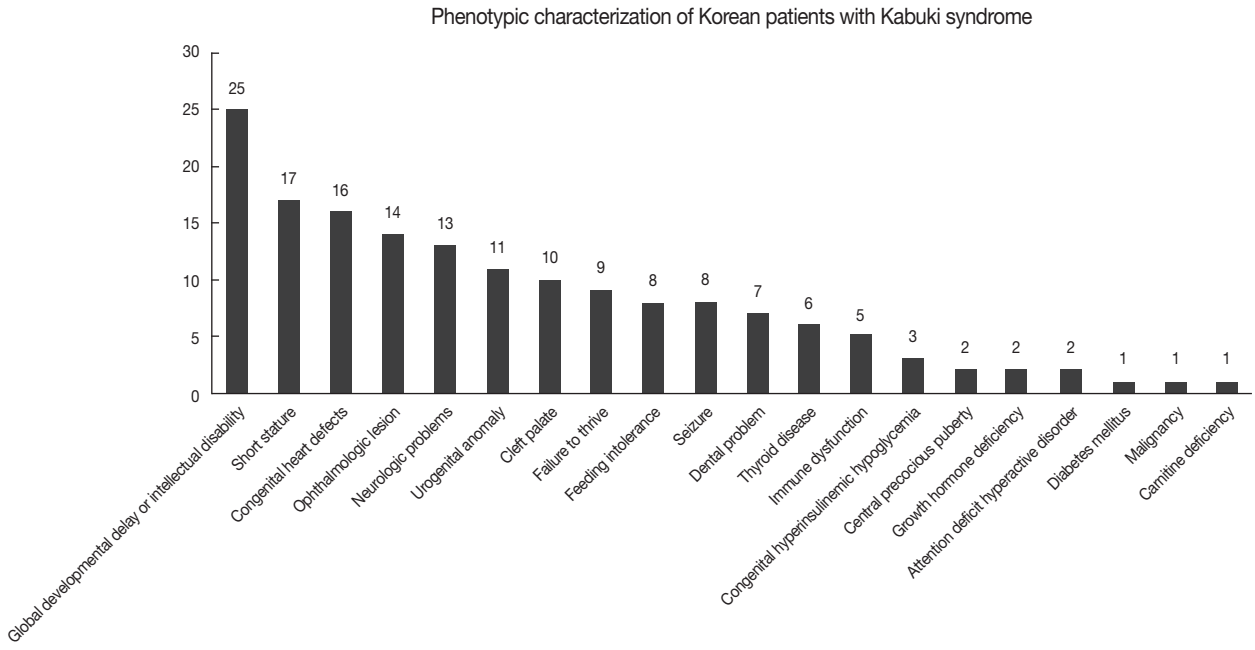


Fig. 3. Comprehensive phenotypic characterization of Korean patients with Kabuki syndrome, highlighting the multisystemic involvement and the extensive spectrum of clinical manifestations.

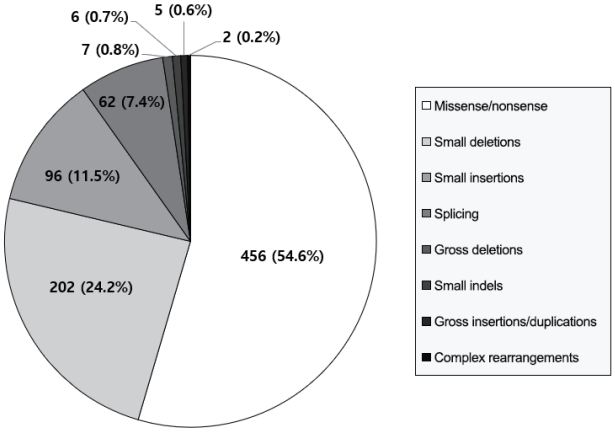


Fig. 4. Distribution of *KMT2D* variant frequencies, encompassing previously reported mutations cataloged in the HGMD alongside 18 novel variants identified in the present study.

gests that *KMT2D* variants may impair growth via disruption of the GH/IGF-1 axis or modulation of SOX9 expression, as demonstrated in animal models [14]. rhGH therapy has shown efficacy in improving linear growth in some KS patients [6,17], although no consensus guidelines currently exist. In our study, among the four patients who received rhGH therapy, two showed favorable growth responses despite the absence of confirmed GH deficiency, suggesting potential benefit in select patients. However, one patient with confirmed GH deficiency had a suboptimal response, emphasizing the need for individualized treatment strategies and further clinical trials to establish therapeutic guidelines in KS.

From a genetic perspective, our study identified a diverse spectrum of *KMT2D* variants, including 18 novel variants. According to the HGMD, over 800 *KMT2D* mutations have been reported to date, encompassing various mutation types such as missense/nonsense variants, small insertions/deletions, and splicing changes. In our cohort, we identified 14 missense/nonsense variants, 4 small deletions, 3 insertions, 1 duplication, and 1 splicing variant—most of which were previously unreported. These novel findings significantly contribute to expanding the mutational landscape of *KMT2D* in KS (Fig. 4).

Interestingly, our analysis revealed a clustering of variants within exons 32, 40, and 49, which accounted for a substantial proportion of both truncating and non-truncating variants. However, unlike previous studies reporting frequent mutations in exons 10, 11, 31, 34, 39, and 48 [18,19], our data suggest a different pattern of mutational hotspots. This discrepancy raises the possibility of ethnic or population-specific variations in *KMT2D* mutation distribution, which warrants validation in larger, multi-ethnic cohorts.

Furthermore, our findings support previous observations suggesting genotype-phenotype correlations. Patients with truncating variants (nonsense and frameshift) exhibited significantly greater involvement of major organ systems compared

to those with non-truncating variants, consistent with prior studies indicating a more severe phenotype associated with loss-of-function mutations [20]. These results emphasize the clinical utility of variant classification in anticipating disease severity and guiding comprehensive, system-based evaluations in affected individuals.

Despite these insights, our study has several limitations. First, 4 of the 27 clinically diagnosed patients (14.8%) lacked identifiable pathogenic variants in *KMT2D* or *KDM6A*. This is in line with prior reports indicating that 20%–45% of KS cases remain genetically unresolved [19]. Additional techniques such as multiplex ligation-dependent probe amplification (MLPA) may uncover larger deletions or duplications not detectable by sequencing. Mosaic variants may also account for some of the unexplained cases, as demonstrated by Montano et al. [21], who identified mosaic *KMT2D* variants in 12 patients (1 novel and 11 previously reported cases). Epigenetic profiling and pyrosequencing analyses may further enhance diagnostic yield in genetically elusive cases [7,13,22].

Second, as this study was conducted at a single institution, the findings may not be generalizable. Future multi-center, prospective studies with larger cohorts are essential to validate genotype-phenotype correlations and better understand the ethnic variability in KS presentation.

This study offers a comprehensive overview of the clinical and genetic characteristics of Korean patients with KS. We identified 18 novel *KMT2D* variants and demonstrated potential genotype-phenotype associations, particularly the more severe clinical features observed in patients with truncating variants. Our findings broaden the mutational spectrum of *KMT2D* and underscore the importance of early recognition, systemic evaluation, and personalized management strategies in KS. Further studies are warranted to refine diagnostic tools and therapeutic approaches, as well as to explore the underlying mechanisms of phenotypic variability in this complex syndrome.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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AUTHOR CONTRIBUTIONS

Conceptualization: Cheon CK. Methodology: Lee J, Cheon CK. Formal analysis: Lee J, Cheon CK. Writing original draft preparation: Lee J, Cheon CK. Writing review: Cheon CK. Supervision: Cheon CK. All authors have read and agreed to the published version of the manuscript.

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Supplementary Table 1. Comparison of clinical features between the mutational hotspots group and the mutational non-hotspots group

	Mutational hotspots group (N=11)	Mutational non-hotspots group (N=12)	*P*-value
Major organ involvements			0.651*
Median (IQR)	5.00 (3)	4.50 (4)	
Congenital heart defects (no., %)	8 (72.7)	6 (50.0)	0.400†
Global developmental delay or intellectual disability (no., %)	10 (90.9)	12 (100)	0.478†
Seizure (no., %)	3 (27.3)	3 (25.0)	>0.99†
Immune dysfunction (no., %)	3 (27.3)	2 (16.7)	0.640†
Short stature (no., %)	8 (72.7)	6 (50.0)	0.400†
Ophthalmologic lesion (no., %)	5 (45.5)	7 (58.3)	0.684†
Urogenital anomaly (no., %)	7 (63.6)	5 (41.7)	0.414†

no., numbers; IQR, interquartile range. *Mann-Whitney U test; †Fisher's exact test.

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4) ***Author contributions***
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