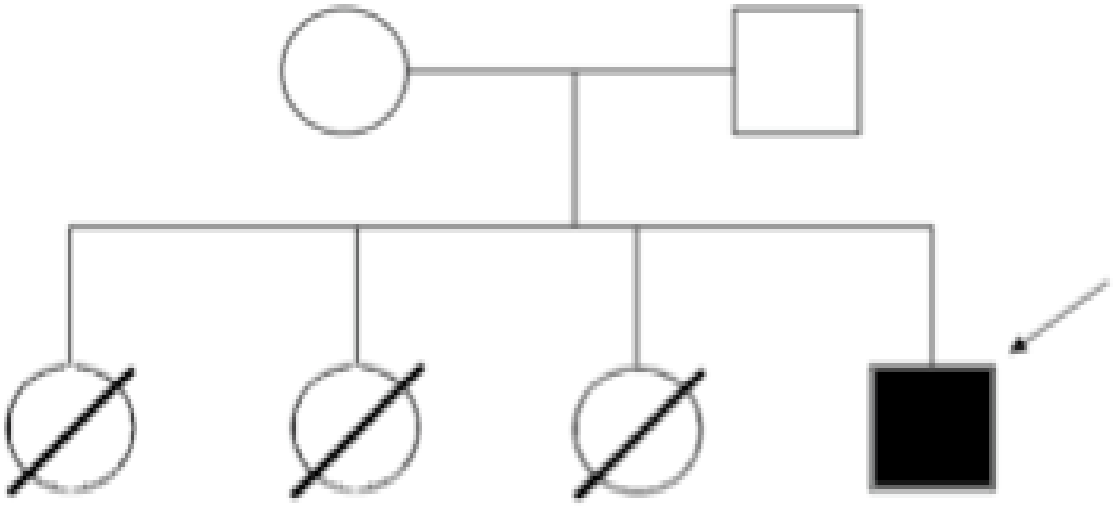
MEDICAL GENETICS INSTITUTE

VIỆN DI TRUYỀN Y HỌC

Teo cơ tuỷ kèm suy hô hấp type 1: SMARD1

ThS.BS : Nguyễn Thuỵ Minh Thư.

BS. Đỗ Phước Huy.



Thai phụ khám tại BV Hùng Vương :
- Tiền căn 3 bé gái mất vì nhược cơ suy hô hấp / IUGR.
- Thai kì lần này : IUGR

⇒1/ Bệnh lý di truyền?
⇒2/ Bệnh lý thần kinh cơ?

Classes of Neuromuscular Diseases

Muscular Dystrophies	Motor Neuron Diseases	Ion Channel Diseases	Mitochondrial Diseases	Myopathies	Neuromuscular Junction Diseases	Peripheral Nerve Diseases
Becker muscular dystrophy (BMD)	Amyotrophic lateral sclerosis (ALS)	Andersen-Tawil syndrome	Friedreich's ataxia (FA)	Congenital myopathies	Congenital myasthenic syndromes (CMS)	Charcot-Marie-Tooth disease (CMT)
Congenital muscular dystrophies (CMD)	Spinal-bulbar muscular atrophy (SBMA)	Hyperkalemic periodic paralysis	Mitochondrial myopathies	Distal myopathies	Lambert-Eaton myasthenic syndrome (LEMS)	Giant axonal neuropathy (GAN)
Duchenne muscular dystrophy (DMD)	Spinal muscular atrophy (SMA)	Hypokalemic periodic paralysis		Endocrine myopathies	Myasthenia gravis (MG)	
Emery-Dreifuss muscular dystrophy (EDMD)		Myotonia congenita		Inflammatory myopathies		
Facioscapulo-humeral muscular dystrophy (FSHD)		Paramyotonia congenita		Metabolic myopathies		
Limb-girdle muscular dystrophy (LGMD)		Potassium-aggravated myotonia		Myofibrillar myopathies (MFM)		
Myotonic dystrophy (DM)				Scapuloperoneal myopathy		
Oculopharyngeal muscular dystrophy (OPMD)						

Source: MDA Classification of Diseases, Jul 2018

Note: Diseases listed are exemplary diseases or groups of diseases from each category. This classification of diseases by MDA does not include malignant hyperthermias, hereditary cardiomyopathies or hereditary paraplegias, which are also considered to be neuromuscular diseases. A full list of neuromuscular diseases with causes known to be found in the nuclear genome can be found at www.musclegenetable.fr and a list of known mitochondrial polymorphisms and mutations of human mitochondrial DNA, and associated known pathologies, can be found at www.mitomap.org.

Report: Understanding Neuromuscular Disease Care: Current State and Future Prospects. IQVIA Institute for Human Data Science, Oct 2018

Bệnh teo cơ tuỷ sống (SMAs):

- Nhóm bệnh lý thần kinh cơ có tính chất di truyền
- Phá huỷ tế bào vận động ở sừng trước tuỷ sống => mất dần chức năng các cơ chi phối.

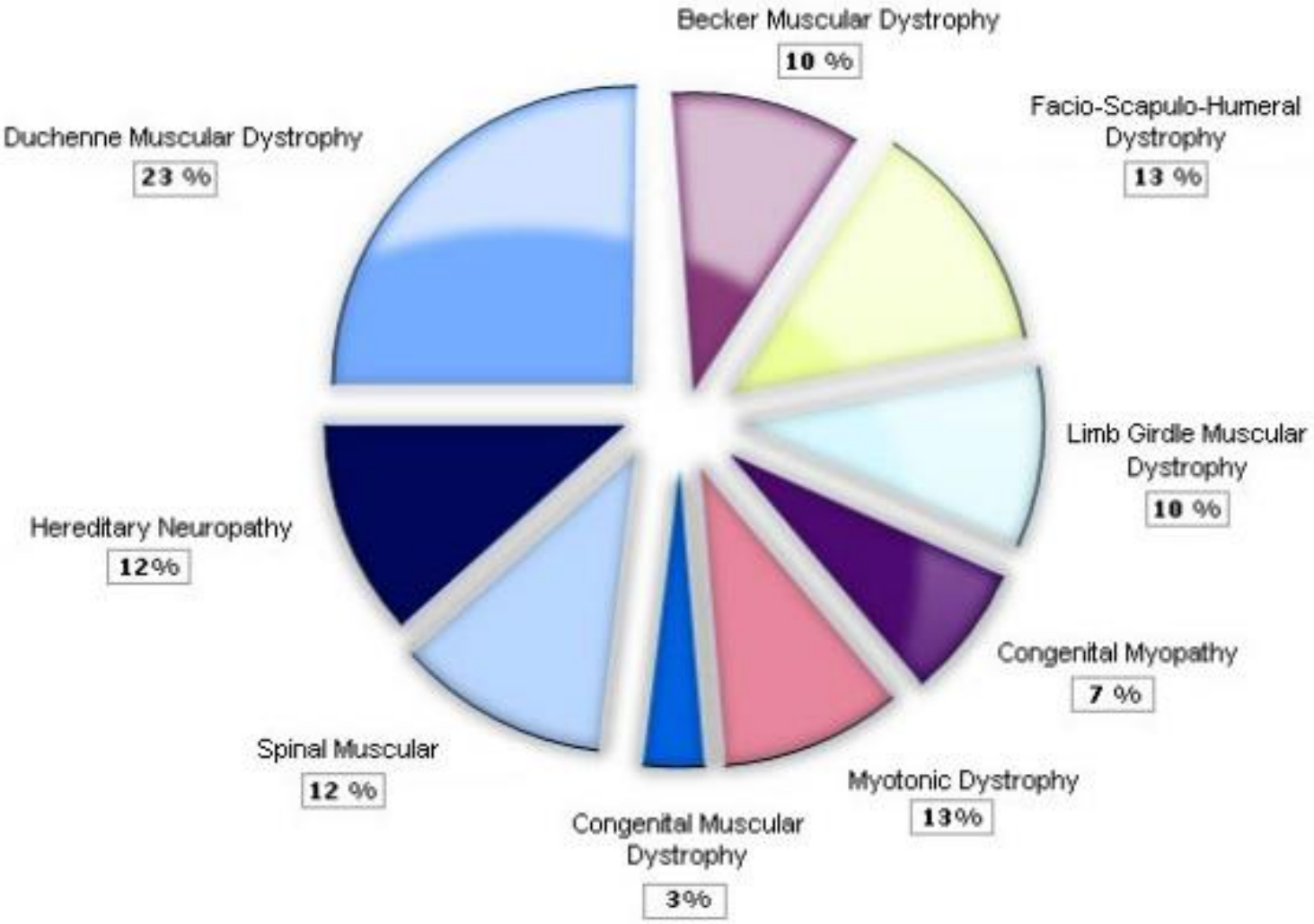
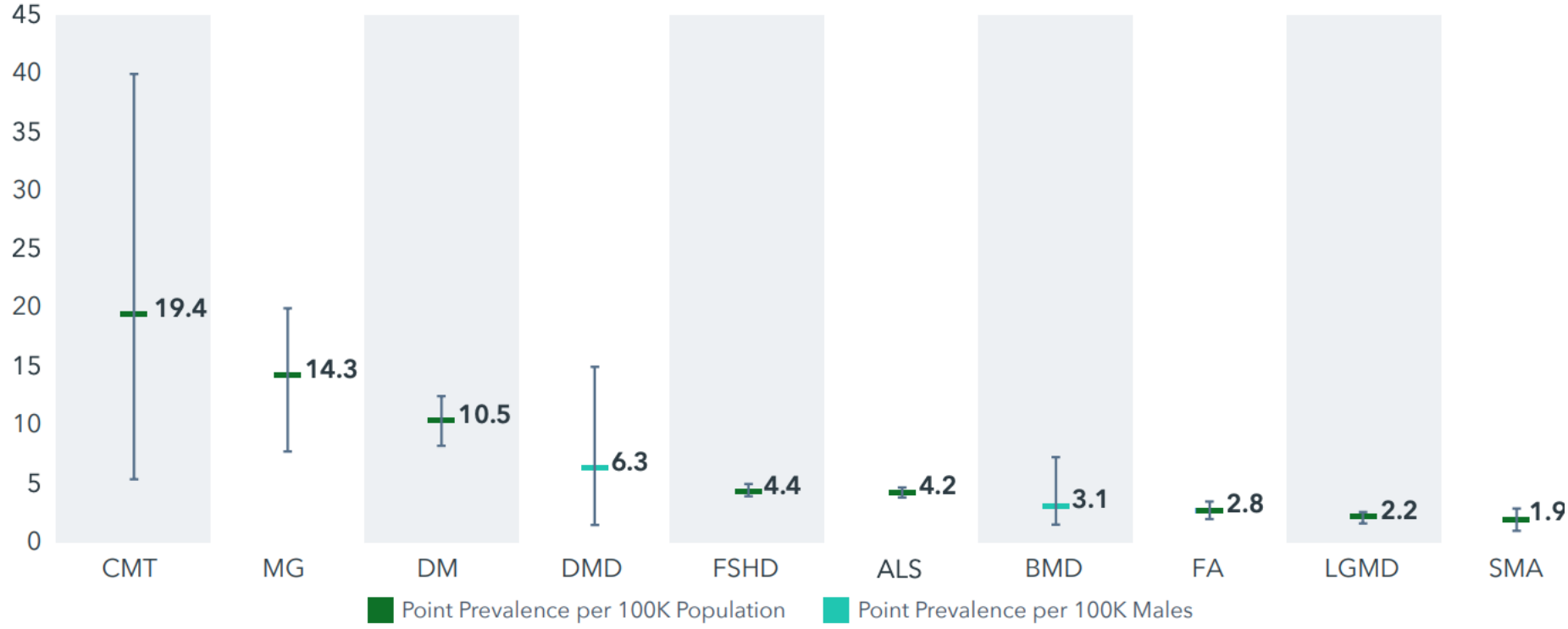

Becker Muscular Dystrophy
10 %
Facio-Scapulo-Humeral Dystrophy
13 %
Limb Girdle Muscular Dystrophy
10 %
Congenital Myopathy
7 %
Myotonic Dystrophy
13%
Congenital Muscular Dystrophy
3%
Spinal Muscular
12 %
Hereditary Neuropathy
12%
Duchenne Muscular Dystrophy
23 %

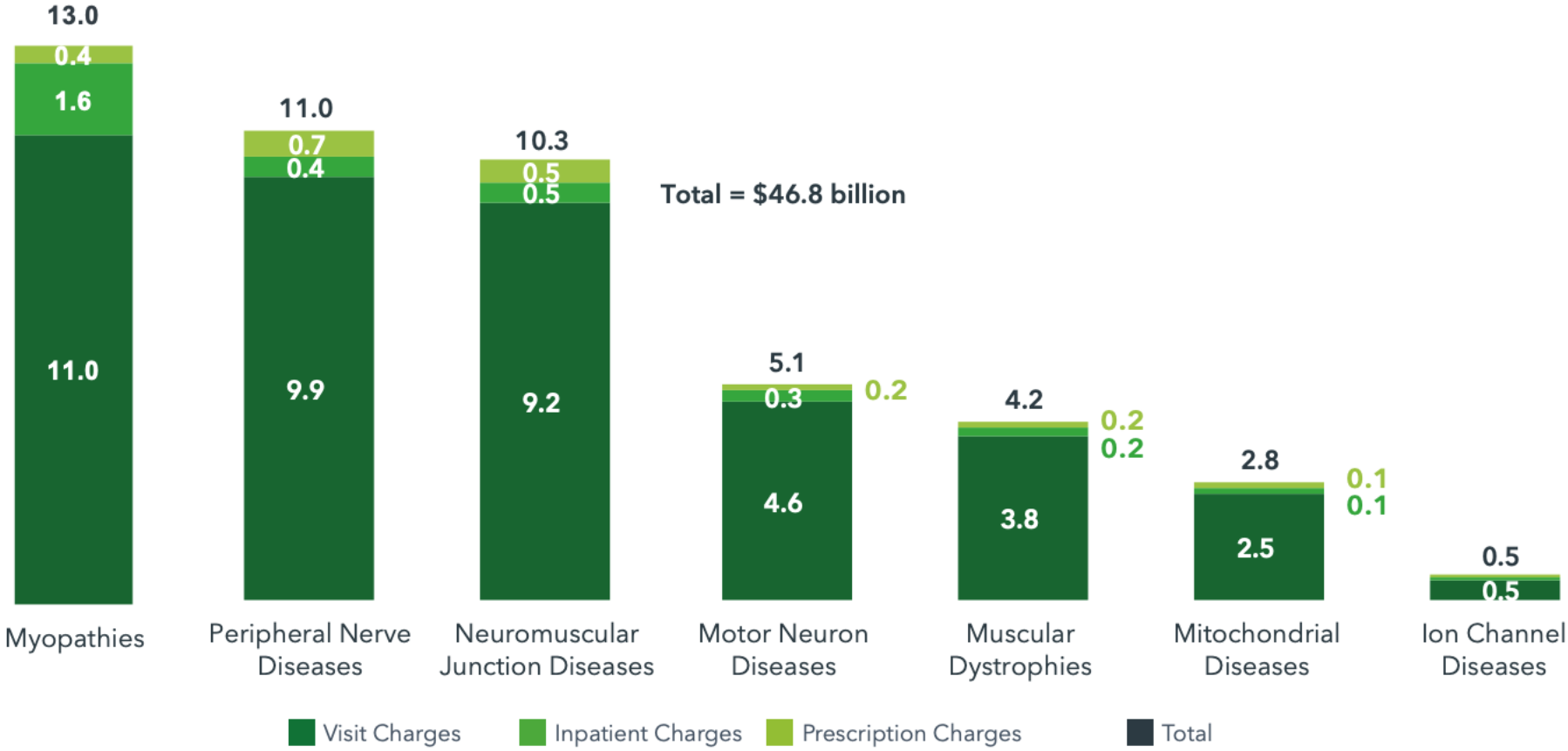
Exhibit 2: Prevalence Estimates Across Neuromuscular Diseases per 100,000 Individuals



Source: Published Literature, see Appendix Table 1

Notes: Data includes prevalence estimates for both United States and ex-United States. Detail on origins of estimates are included in Appendix Table 1. Neuromuscular diseases not plotted have no identified reliable point prevalence estimates available. Mitochondrial myopathies are thought to affect approximately 6 per 100,000, all other disease are thought to affect <1 in 100,000 individuals. Estimates for DMD and BMD, which are tied to X-linked mutations are reported per 100 thousand males. Dotted lines denote range of included estimates. CMT = Charcot-Marie-Tooth syndrome, DM = myotonic dystrophy, MG = myasthenia gravis, DMD = Duchenne muscular dystrophy, FSHD = facioscapulohumeral muscular dystrophy, ALS = amyotrophic lateral sclerosis, BMD = Becker muscular dystrophy, LGMD = limb-girdle muscular dystrophy, FA = Friedreich's ataxia, SMA = spinal muscular atrophy.

Exhibit 4: Average Total Annual Medical Charges per Disease Group, Un-projected Data US$Bn



Source: IQVIA Real World Data (RWD) including Medical Claims and Prescription Datasets, July 2018; IQVIA Institute, July 2018

Notes: Shows the average of annual un-projected medical charges for two years Jul 2015-Jul 2017. Total charges depicted per disease group are driven by both the number of patients as well as cost per patient. Excludes some costs such as those for over-the-counter medicines that would not go through claims processing. Total annual charges for the entire U.S. population are expected to be higher, while adjudicated costs may be higher or lower than depicted. Un-projected Medical Claims Data is estimated to represent 60% of patients in the United States. Unadjudicated charges exceed amount reimbursed by payers, and are estimated to range from 40-60% depending on payer type. Prescription charged are estimated to represent 90.2% of the U.S. market across retail, mail, and long term care channels of distribution. Methodologically, if any patients had multiple diagnoses within two or more disease groups, their charges would be counted once in each group.

Phân loại:

- Dựa theo nhóm cơ bị ảnh hưởng : Gốc chi – ngọn chi
- Bất thường về di truyền : bất thường NST 5 hay không.

Table 1 Types of spinal muscular atrophy in humans (modified from [55])

SMA type	Inheritance	Gene/location	Phenotype/symptoms	Age at onset
SMA-1	AR	*SMN1*/5q11.2–13.3	Proximal muscle weakness, never sit unaided, death usually <2 years	Usually <9 months
SMA-2	AR	*SMN1*/5q11.2–13.3	Proximal muscle weakness, sit unaided but wheelchair bound, most survive to 2nd or 3rd decade	6–18 months
SMA-3	AR	*SMN1*/5q11.2–13.3	Proximal muscle weakness, walk unaided, slow progression with normal lifespan	Usually >48 months
Distal SMA	AR	11q13	Distal muscle weakness, involvement of diaphragm	2 months–20 years
SMARD	AR	*IGHBP2*/11q13.2	Distal lower limb and diaphragmatic weakness, sensory and autonomic neurons also affected	1–6 months
X-linked infantile SMA	X-linked	Xp11.3-q11.2	Arthrogryposis, respiratory insufficiency, scoliosis, chest deformities, LMN loss	At birth
Spino-bulbar SMA (Kennedy disease)	X-linked	Androgen receptor/Xq11.2–12	Proximal muscle weakness, LMN loss, loss of neurons in dorsal root ganglia, bulbar involvement	30–50 years
Distal SMA-4	AD	7p15	Distal muscle weakness of thenar and peroneal muscles	12–36 years
Congenital SMA	AD	12q23–24	Arthrogryposis, non-progressive weakness of distal muscles of lower limbs	At birth
SMA associated with mitochondrial mutation	Mitochondrial	Cytochrome-c oxidase (COX)	Hypotonia, lactic acidosis, respiratory distress, cardiomyopathia, COX deficiency	At birth

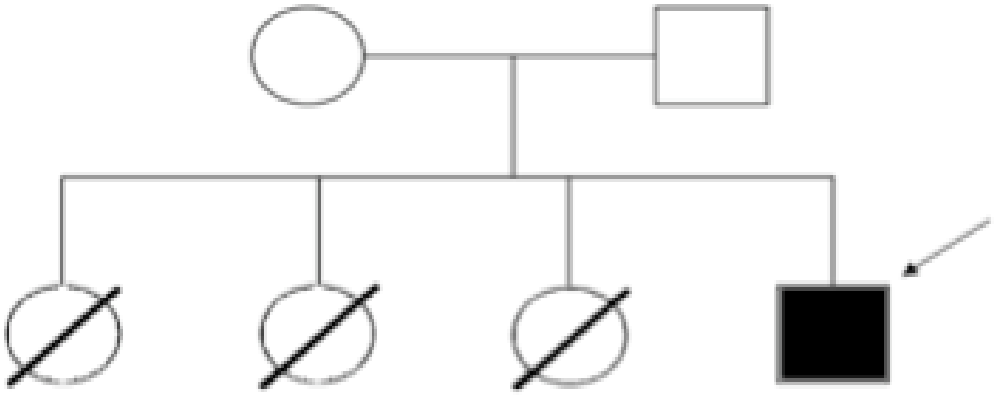
Simic, G. (2008). Pathogenesis of proximal autosomal recessive spinal muscular atrophy. Acta Neuropathologica, 116(3), 223–234.

Ca lâm sàng

- Bé trai 6 tháng tuổi nhập viện vì suy hô hấp :

- Con 4/4, sinh 2200g, sinh thường đủ tháng. Khóc ngay sau sanh.
- Mẹ thiểu ối khi có thai.

Tiền căn gia đình :



- Con ¼ : Nữ, đủ tháng, CNLS 1600g, tay chân nhỏ. Mất 4d sau sanh.
- Con 2/4 : Nữ, đủ tháng, CNLS 2200g, chậm phát triển tâm vận, tay chân nhỏ. Mất lúc 2 tuổi vì khò khè khó thở.
- Con ¾ : Nữ, 30w, CNLS 1000g, chậm phát triển tâm vận, tay chân nhỏ, co quắp. Mất lúc 18 tháng vì khò khè khó thở.

- Chậm phát triển vận động.
- Chu vi vòng đầu : 35cm
- Sức cơ 4/5
- Bàn chân dị hình , kích thước nhỏ.

Kết quả cận lâm sàng :

+ X-Quang ngực thẳng : Vòm hoành P nâng cao

+ MSMS : bình thường.

+ Khí máu động mạch :

+ Các chỉ số khác: Trong giới hạn bình thường.

+ Chưa làm xét nghiệm DMD, SMA.

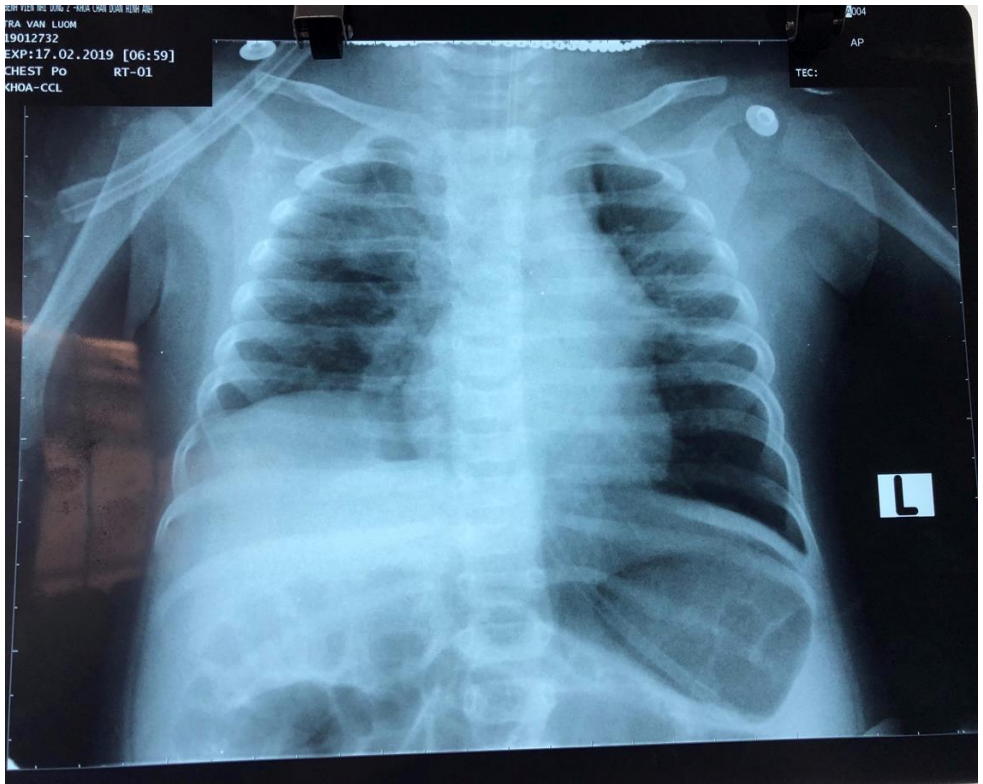


Table 1. Symptoms of SMARD1 Infants and Age of Onset

Feature	No./Total No. (infants) (%)	Median (mo)	Interquartile Range	Range
Respiratory system				
Inspiratory stridor	7/14 (50)	0.5	2.8	0.0–5.1
Weak cry	21/21 (100)	1.0	2.6	0.0–5.6
Respiratory distress	29/29 (100)	3.0	3.2	0.1–12.0
Poor feeding	15/26 (58)	3.0	3.4	0.0–6.6
Respiratory failure	29/29 (100)	3.5	3.7	1.0–13.2
Neuromuscular system				
Foot deformities	19/22 (86)	1.5	6.3	0.0–24.3
Muscular hypotonia	22/27 (82)	1.8	6.0	0.0–10.1
Limb weakness distally marked	19/22 (86)	4.0	4.4	0.0–13.2
Tendon reflexes absent	18/21 (86)	4.0	3.8	0.0–42.6
Finger contractures	7/17 (41)	4.5	9.1	0.0–16.2
Cranial nerves				
Facial weakness	5/16 (31)	10.1	16.1	3.0–24.3
Tongue fasciculations	6/17 (35)	11.4	16.4	6.0–32.6
Sensory and autonomic nervous systems				
Decreased pain perception	3/11 (27)	6.6	—	5.0–10.1
Excessive sweating	7/12 (58)	5.0	1.0	3.0–68.2
Constipation	8/15 (53)	5.0	19.1	0.0–48.7
Bladder incontinence	5/10 (50)	12.0	10.2	2.0–16.2
Cardiac arrhythmia	5/7 (71)	—	—	—

Grohmann, K., Varon, R., Stolz, P., Schuelke, M., Janetzki, C., Bertini, E., … Hübner, C. (2003). Infantile spinal muscular atrophy with respiratory distress type 1 (SMARD1). Annals of Neurology, 54(6), 719–724.

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Diagnostics & Cures

KẾT QUẢ PHÂN TÍCH ĐỘT BIẾN GEN

THÔNG TIN BỆNH NHÂN

Họ tên:	[redacted]	**Giới tính:**		**Ngày sinh:**	6 tháng tuổi
Ký hiệu mẫu:	G0605			**Điện thoại:**	
Ngày thu mẫu:	22/02/2019	**Nơi thu mẫu:**	BVHV		
Mẫu:	Máu	**Bác sĩ chỉ định:**	Nguyễn Thị Thanh Trúc		
Thông tin lâm sàng:	Chậm phát triển, suy hô hấp, yếu chi. 3 anh chị mất vì suy hô hấp				

KẾT QUẢ

Gen	Dạng di truyền	Biến thể phát hiện	Đồng hợp/ dị hợp
IGHMBP2	Lặn	NM_002180.2(IGHMBP2):c.1813C>T (p.Arg605Ter) NM_002180.2(IGHMBP2):c.1334A>C(p.His445Pro)	Dị hợp kép
IGHMBP2	Lặn		

KẾT LUẬN: Phát hiện đột biến dị hợp kép trên gene *IGHMBP2*.

NM_002180.2(IGHMBP2):c.1334A>C (p.His445Pro) : Not reported in ClinVar

Bệnh teo cơ tủy sống kèm nguy kịch hô hấp (SMARD1, OMIM #604320)

Distal spinal muscular atrophy type 1 (DSMA1) is an autosomal recessive disease that is clinically characterized by distal limb weakness and respiratory distress. In this disease, the degeneration of α-motoneurons is caused by mutations in the immunoglobulin μ-binding protein 2 (IGHMBP2). This protein has been implicated in DNA replication, pre-mRNA splicing and transcription, but its precise function in all these processes has remained elusive. We have purified catalytically active recombinant IGHMBP2, which has enabled us to assess its enzymatic properties and to identify its cellular targets. Our data reveal that IGHMBP2 is an ATP-dependent 5′→3′ helicase, which unwinds RNA and DNA duplices *in vitro*. Importantly, this helicase localizes predominantly to the cytoplasm of neuronal and non-neuronal cells and associates with ribosomes. DSMA1-causing amino acid substitutions in IGHMBP2 do not affect ribosome binding yet severely impair ATPase and helicase activity. We propose that IGHMBP2 is functionally linked to translation, and that mutations in its helicase domain interfere with this function in DSMA1 patients.

Guenther, U.-P., Handoko, L., Laggerbauer, B., Jablonka, S., Chari, A., Alzheimer, M., … Fischer, U. (2009). IGHMBP2 is a ribosome-associated helicase inactive in the neuromuscular disorder distal SMA type 1 (DSMA1). Human Molecular Genetics, 18(7), 1288–1300.

Bệnh teo cơ tủy sống kèm nguy kịch hô hấp (SMARD1, OMIM #604320)

Genetics Home Reference | Your Guide to Understanding Genetic Conditions

Frequency

SMARD1 appears to be a rare condition, but its prevalence is unknown. More than 60 cases have been reported in the scientific literature.

Table 1 Diagnostic criteria proposed by Pitt *et al.* to allow a more accurate diagnosis of SMARD1 and to help distinguish it from other similar conditions (Pitt et al. 2003)

Clinical criteria	Histopathological criteria	EMG criteria
Low birth weight <3rd percentile	Reduced myelinated fibre diameter in sural nerve biopsies*	Evidence of acute or chronic distal denervation
Onset of symptoms within the first 3 months of life	Slight evidence of progressive myelinated fibre degeneration in biopsies taken up to 3–4 months	Evidence of significant slowing (<70% of LLN) in one or more motor a/o sensory nerves
Unilateral or bilateral diaphragmatic weakness	No evidence of regeneration nor demyelination, that could justify the reduction in fibre size	
Ventilator dependence within <1 month of onset associated to inability to wean		
No evidence of other dysmorphology or other conditions		

Available online at www.sciencedirect.com

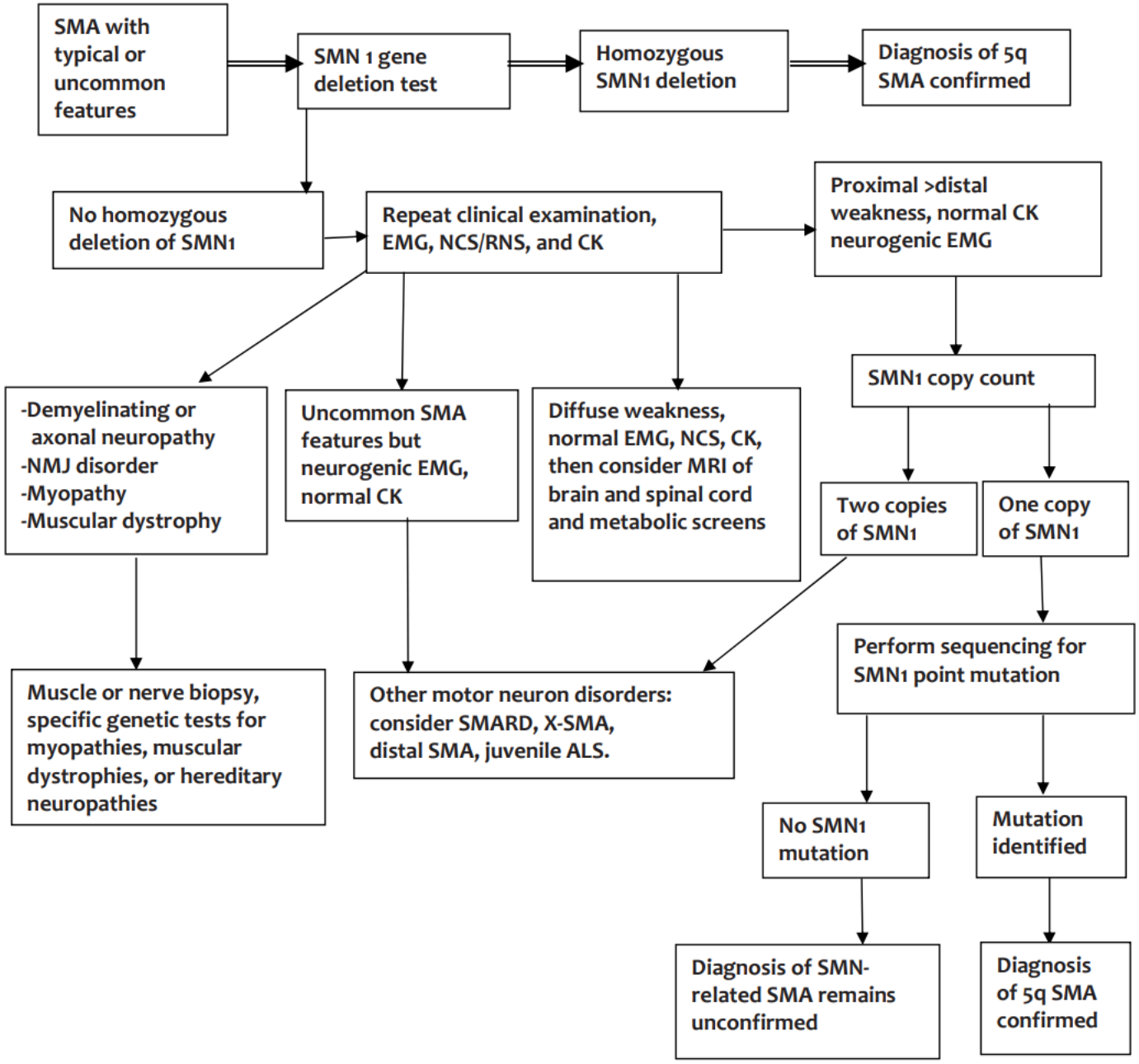
Clinical criteria
Low birth weight <3rd percentile
Onset of symptoms within the first 3 months of life
Unilateral or bilateral diaphragmatic weakness
Ventilator dependence within <1 month of onset associated to inability to wean
No evidence of other dysmorphology or other conditions

Our findings enhance and challenge the diagnostic criteria published by Pitt et al. in 2003 [23] and the algorithm of Guenther et al. from 2007 [14]. For example, we observed that many cases from our cohort would have been excluded according to items (i) (ii) and (iv) (see Table 1, column "Clinical criteria") although their genotype, phenotype and natural course matched with others. More specifically, IUGR under the 10th percentile seems less restrictive than the 3rd percentile (60 vs. 45%), 31.8% developed symptoms after 3 months of age, and ventilator dependence occurred mostly (78.6%) after one month of disease evolution.

Florence Petit[a], Corinne Magdelaine[j], Fabienne Giuliano[p], Domitille Gras[q], Damien Haye[r], Mathilde Nizon[s], Maryse Magen[s], Eric Bieth[t], Claude Cances[a]

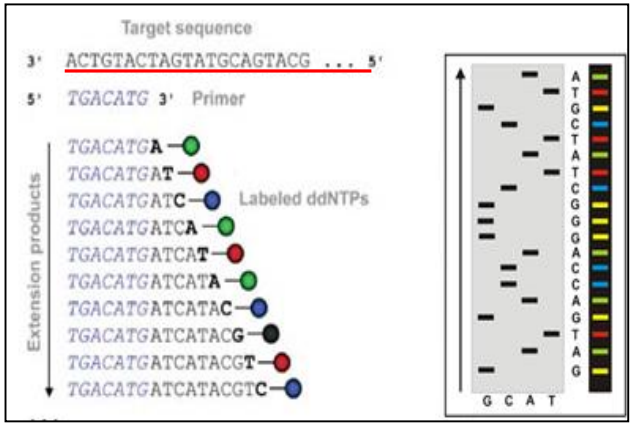
belatedly after the respiratory symptoms. Thus, rather than waiting for the occurrence of phrenic palsy to raise the possibility of SMARD1, practitioners should order genetic testing, keeping in mind that this feature will very likely appear at some point. This delay might be explained by an early but progressive phrenic palsy causing weak cry and feeding difficulties, followed by respiratory symptoms and ultimately radiographic evidence. A trigger factor, like an infection, could hasten acute respiratory failure. In the meantime, there are

Fig. 1 Diagnostic Evaluation for Spinal Muscular Atrophy



Giải trình tự gen thế hệ mới (NGS/MPS)

Giải trình tự Sanger

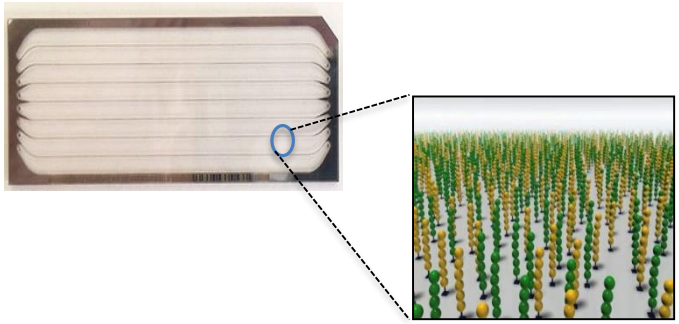


1 đoạn DNA/mỗi phản ứng

Chi phí: $2.400/1Mb

Giải trình tự thế hệ mới

(Next-generation sequencing = ***Massive parallel sequencing*****)**



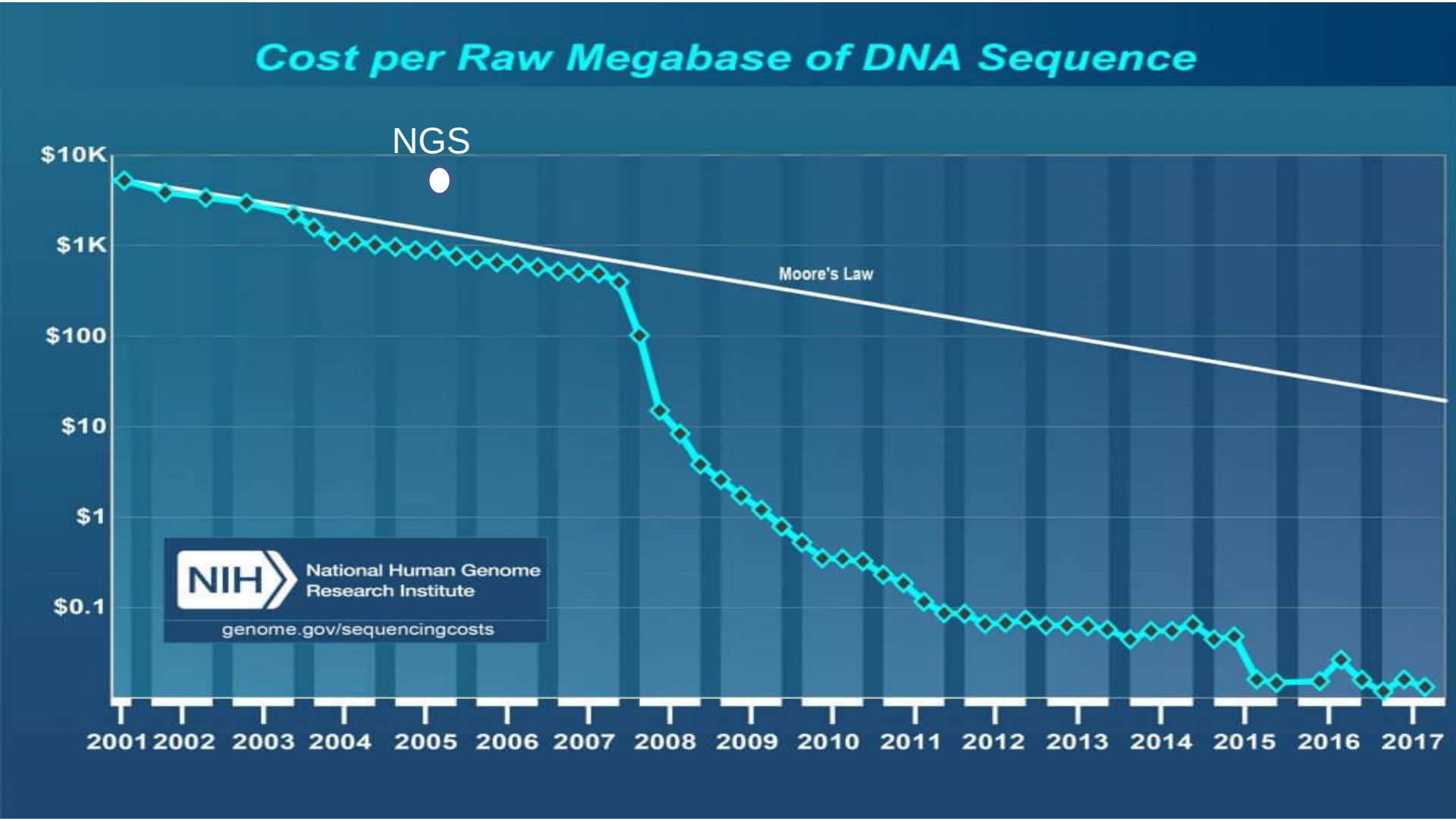
Hàng triệu đoạn DNA/mỗi phản ứng

Chi phí: $0.5/1Mb

MiniSeq (50 triệu DNA -7.5 Gb)

NextSeq (800 triệu DNA -120 Gb)

CHI PHÍ GIẢI TRÌNH TỰ



Chi phí giải trình tự giảm >1 triệu lần trong 10 năm

Genetic Testing in Neuromuscular Disorders

Understanding ordering and interpretation of genetic tests is paramount for clinical management.

By James P. Orengo, MD, PhD and David R. Murdock, MD

TABLE. TYPES OF GENETIC TESTING AVAILABLE

	Sanger	Panel	Mitochondrial DNA	Whole-exome sequencing	Whole-genome sequencing
Technology	Chain termination	NGS	NGS	NGS	NGS
Genes tested	Single	Few-hundreds	37 (mitochondrial genome)	20,000 (coding only)	20,000 (coding and non-coding)
Cost	$$	$	$$	$$	$$$
Variants detected	SNV, InDel	SNV, InDel, CNV	SNV, InDel	SNV, InDel	SNV, InDel, CNV, Repeats
Potential VUS	+	++	+	+++	+++++

Abbreviations: CNV, copy number variation; InDel, small insertions and deletions; NGS, next-generation sequencing; Repeats, repeat expansions; SNV, single nucleotide variant; VUS, variant of uncertain significance.

FDA NEWS RELEASE

FDA approves first drug for spinal muscular atrophy

For Immediate Release:

December 23, 2016

The U.S. Food and Drug Administration today approved Spinraza (nusinersen), the first drug approved to treat children and adults with spinal muscular atrophy (SMA), a rare and often fatal genetic disease affecting muscle strength and movement. Spinraza is an injection

U.S. FOOD & DRUG ADMINISTRATION

FDA NEWS RELEASE

FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality

For Immediate Release:

May 24, 2019

The U.S. Food and Drug Administration today approved Zolgensma (onasemnogene abeparvovec-xioi), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and a leading genetic

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

E. Mercuri, B.T. Darras, C.A. Chiriboga, J.W. Day, C. Campbell, A.M. Connolly, S.T. Iannaccone, J. Kirschner, N.L. Kuntz, K. Saito, P.B. Shieh, M. Tulinius, E.S. Mazzone, J. Montes, K.M. Bishop, Q. Yang, R. Foster, S. Gheuens, C.F. Bennett, W. Farwell, E. Schneider, D.C. De Vivo, and R.S. Finkel, for the CHERISH Study Group*

Molecular Therapy
Methods & Clinical Development
Original Article

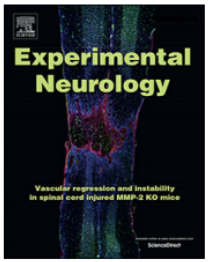
A Direct Comparison of IV and ICV Delivery Methods for Gene Replacement Therapy in a Mouse Model of SMARD1

Experimental Neurology 321 (2019) 113041

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

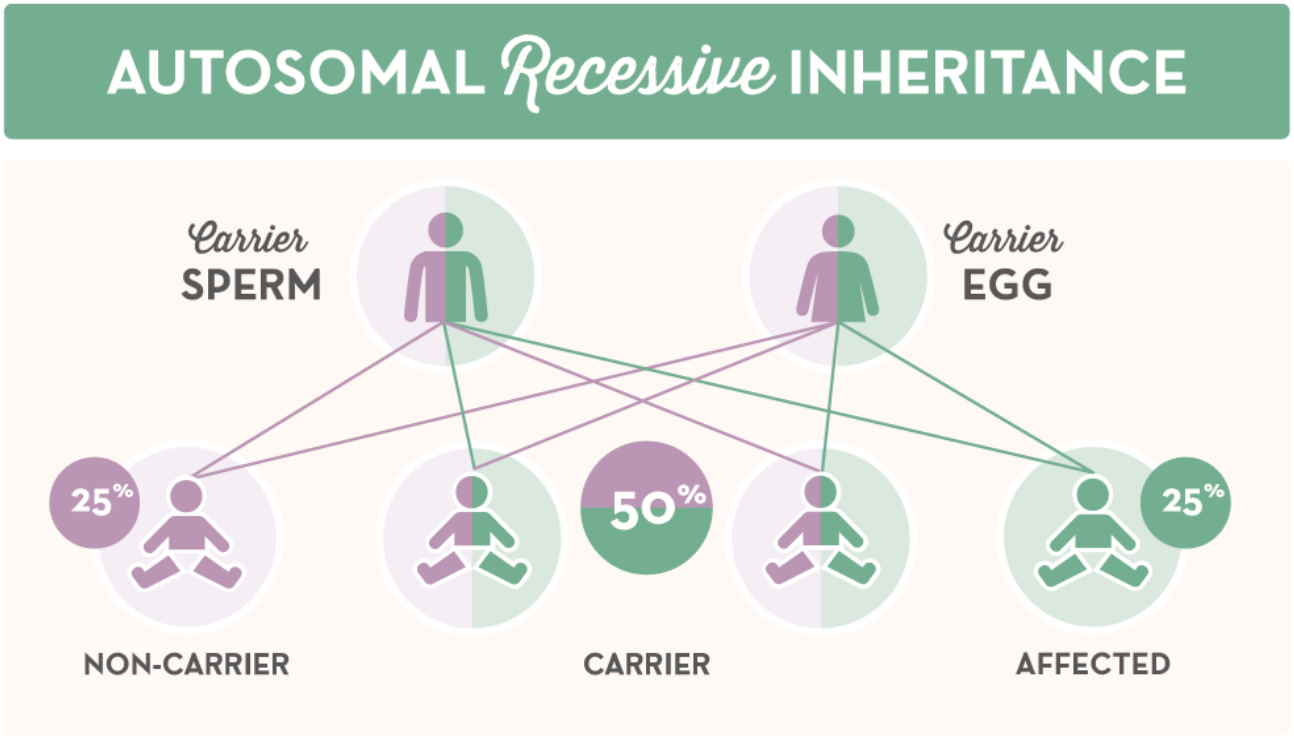


Research Paper

CSF transplantation of a specific iPSC-derived neural stem cell subpopulation ameliorates the disease phenotype in a mouse model of spinal muscular atrophy with respiratory distress type 1

Giulia Forotti[a,1], Monica Nizzardo[a,1], Monica Bucchia[b], Agnese Ramirez[b], Elena Trombetta[c], Stefano Gatti[d], Nereo Bresolin[a,b], Giacomo Pietro Comi[a,b,2], Stefania Corti[a,b,*,2]

[a] Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[b] Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Italy
[c] Flow Cytometry Service, Analysis Laboratory, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[d] Center for Surgical Research, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy



Nguy cơ tái mắc 25%

⇒ Sàng lọc – lên kế hoạch cho thai kỳ sau :

+ Chẩn đoán tiền làm tổ (PGT).

+ Chẩn đoán tiền sinh.

Kết luận

- SMARD1 là một bệnh lý di truyền hiếm và chưa có phương pháp điều trị đặc hiệu.
- Xét nghiệm di truyền học tìm đột biến trên gene IGHMBP2 giúp cho chẩn đoán và tiên lượng cho thai kỳ sau.
- Tư vấn di truyền có vai trò quan trọng với những bệnh lý di truyền nghiêm trọng.

XIN CHÂN THÀNH CẢM ƠN :

TS.BS Nguyễn Lê Trung Hiếu. (BV. Nhi Đồng 2)
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CHÂN THÀNH CẢM ƠN
SỰ CHÚ Ý LẮNG NGHE