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# 精準醫療於遺傳性疾病

## Precision Medicine in Genetic Disease

時　　間：113 年 6 月 22 日(星期六) 08:30~17:30
地　　點：臺北榮民總醫院 致德樓第一會議室

| Time | Topic & Speaker | Moderator |
|---|---|---|
| **08:30-08:40** | ***Opening*** | |
| 08:40-09:10 | 法布瑞氏症的基因治療<br>Gene Therapy for Fabry Disease<br>*Prof. Michael West (Canada)* | 魏耀揮教授<br>*Prof. Yau-Huei Wei* |
| 09:10-09:40 | 基因治療併發症的預防與治療<br>Prevention and Treatment of Complications in Gene Therapy<br>王馨慧教授 *Prof. Hsin-Hui Wang* | 林清淵教授<br>*Pro.Ching-Yuang Lin* |
| 09:40-10:10 | Pegunigalsidase alfa：一種新型的聚乙二醇化重組α-半乳糖苷酶，用於治療法布瑞氏症<br>Pegunigalsidase Alfa: A novel, pegylated Recombinant Alpha-Galactosidase Enzyme for the Treatment of Fabry Disease<br>*Prof. Dominique P. Germain (France)* | 鄭敬楓教授<br>*Prof. Ching-Feng Cheng* |
| 10:10-10:30 | 法布瑞氏症心臟切片中不可逆轉細胞損傷的早期檢測：Gb3包涵體形成前的觀察<br>Early Detection of Irreversible Cellular Damage in Cardiac Biopsies of Fabry Disease Before the Formation of Gb3 Inclusion Bodies<br>牛道明教授 *Prof. Dau-Ming Niu* / 李忠霖醫師 *Dr. Chung-Lin Lee* | 褚柏顯教授<br>*Prof. Pao-Hsien Chu* |
| **10:30-10:50** | ***Discussion* 黃奇英教授 *Prof. Chi-Ying Huang* 殷偉賢教授 *Prof. Wei-Hsian Yin*** | |
| **10:50-11:00** | ***Coffee Break*** | |
| 11:00-11:30 | 日本溶酶體儲積症的新生兒篩檢及治療現況<br>Newborn Screening and Treatment of Lysosomal Storage Diseases in Japan<br>*Prof. Kimitoshi Nakamura (Japan)* | 趙美琴教授<br>*Prof. Mei-Chyn Chao* |
| 11:30-12:00 | 越南龐貝氏症診斷、酵素替代療法以及脊髓肌肉萎縮症的基因替代療法的最新進展<br>Update on Diagnosis, Enzyme Replacement Therapy for Pompe Disease And Gene Replacement Therapy for Spinal Muscular Atrophy in Vietnamese Patients<br>*Prof. Vu Chi-Dung (Vietnam)* | 陳燕彰教授<br>*Prof. Yann-Jang Chen* |

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|---|---|---|
| **12:00-12:10** | ***Discussion* 遲景上教授 *Prof. Ching-Shiang Chi* 林秀娟教授 *Prof. Shio-Jean Lin*** | |
| **12:10-13:30** | ***Lunch*** | |
| 13:30-14:00 | 新生兒基因組篩檢的全球進展<br>Global Advancements in Newborn Genomic Screening<br>*Executive Director of ICoNS Nicolas Encina (USA)* | 陳鴻震教授<br>*Prof. Hong-Chen Chen* |
| 14:00-14:30 | 全基因體 / 全外顯子定序即時分析系統在臨床上的應用<br>Applications of a Rapid Real Time Analysis System for Whole Genome / Exome Sequencing to Clinicians<br>牛道明教授 *Prof. Dau-Ming Niu* | 黃朝慶教授<br>*Prof. Chao-Ching Huang* |
| 14:30-15:00 | 癌症基因體的全面分析<br>Comprehensive Analysis of Whole Cancer Genome<br>張建國教授 *Prof. Jan-Gowth Chang* | 潘競成教授<br>*Prof. Chin-Chen Pan* |
| **15:00-15:20** | ***Discussion* 陳銘雄院長 *Prof. Chih-Hiung Chen* 蔡世峯教授 *Prof. Shih-Feng Tsai*** | |
| **15:20-15:30** | ***Coffee break*** | |
| 15:30-15:50 | 龐貝氏症的現在與未來<br>Pompe Disease: Now and Future<br>楊佳鳳教授 *Prof. Chia-Feng Yang* | 邱寶琴教授<br>*Prof. Pao-Chin Chiu* |
| 15:50-16:10 | 臺灣的黏多醣症第一、二、四 A、六型新生兒篩檢計畫與基因變異之應用<br>Newborn Screening Programs for Mucopolysaccharidoses Types I, II, IVA, and VI in Taiwan and the Application of Gene Variants<br>林翔宇教授 *Prof. Hsiang-Yu Lin* | 郭雲鼎教授<br>*Prof. Yung-Ting Kuo* |
| 16:10-16:30 | 脊髓性肌肉萎縮症的現在與未來<br>Spinal Muscular Atrophy: Now and Future<br>許庭榕教授 *Prof. Ting-Rong Hsu* | 陳錫洲教授<br>*Prof. Shyi-Jou Chen* |
| 16:30-17:00 | 裘馨氏症的現在與未來<br>Duchenne Muscular Dystrophy: Now and Future<br>翁奴謹醫師 *Dr. Wen-Chin Weng* | 李旺祚教授<br>*Prof. Wang-Tso Lee* |
| **17:00-17:20** | ***Discussion* 鐘育志教授 *Prof. Yuh-Jyh Jong* 林炫沛教授 *Prof. Shuan-Pei Lin*** | |
| **17:20** | ***Closing Remarks* 牛道明 教授 *Prof. Dau-Ming Niu*** | |

# Gene therapy for Fabry disease

## 法布瑞氏症的基因治療

**Michael West**

*Division of Nephrology, Department of Medicine, Dalhousie University & Nova Scotia Health, Canada*

*加拿大達爾豪斯大學 醫學系 腎臟科*

Gene therapy is the delivery of a therapeutic gene for endogenous cellular expression with the goal of rescuing a disease phenotype. It has been used to treat an increasing number of human diseases with many strategies proving safe and efficacious in clinical trials. Gene delivery may be viral or non-viral, performed in vivo or ex vivo, and relies on gene integration or transient expression; all of these techniques have been applied to the treatment of Fabry disease.

Fabry disease is a genetic disorder of the α-galactosidase A gene, *GLA*, that causes an accumulation of glycosphingolipids in cells leading to cardiac, renal and cerebrovascular damage and eventually death. Currently, there are no curative treatments available, and the therapies that are used have significant drawbacks. These treatment concerns have led to the advent of gene therapies for Fabry disease. The first Fabry patients to receive gene therapy were treated with recombinant lentivirus targeting their hematopoietic stem/progenitor cells. Adeno-associated virus treatments have also begun. Alternatively, the field of gene-editing is a new and rapidly growing field. Gene-editing has been used to repair disease-causing mutations or insert genes into cellular DNA. These techniques have the potential to be applied to the treatment of Fabry disease provided the concerns of gene-editing technology, such as safety and efficiency, were addressed. This talk will discuss the current state of gene therapy as it is being developed for Fabry disease, including progresses and challenges as well as an overview of gene-editing and how it may be applied to correct Fabry disease-causing mutations in the future.

# Prevention and treatment of complications in gene therapy

# 基因治療併發症的預防與治療

**Hsin-Hui Wang**

**王馨慧**

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Gene therapy has great potential to treat genetic diseases, but it also faces significant challenges that require careful management to ensure patient safety and therapeutic efficacy. It is critical to address complications such as safety risks, genotoxicity, immunogenicity, and toxicity.

Efforts are ongoing to develop safer vehicles and to personalize delivery routes based on individual characteristics. Strategies to modulate immunity play a key role in minimizing immunogenicity-related problems, while controlling complications through symptom control, dose adjustment, or targeted therapy requires immediate intervention.

Although site-specific gene editing approaches can reduce risks, genotoxicity remains a concern, especially for viral vectors. Despite advances, gene-editing technologies still carry inherent genotoxic risks. Immunogenicity poses challenges, particularly with AAV-based therapies, where pre-existing immunity may hinder efficacy. Therefore, strategies to overcome immune responses are imperative. Toxicity, including hepatotoxicity and thrombotic microangiopathy (TMA), requires vigilant monitoring and management. Optimizing vector design, dosing regimen, and immune modulation are key strategies to prevent and mitigate toxicity. Approaches to mitigate immunogenicity include vector engineering, immunomodulatory drugs, plasma exchange, and enzyme-based antibody cleavage.

Overall, successful gene therapy requires a multidisciplinary approach and ongoing research to optimize vector components, dosing regimens, and immunomodulatory strategies. Long-term monitoring and careful management of complications are critical to realizing the full potential of gene therapy and improving patient outcomes.

# Pegunigalsidase alfa: A novel, pegylated recombinant alpha-galactosidase enzyme for the treatment of Fabry disease

# Pegunigalsidase alfa：一種新型的聚乙二醇化重組 α- 半乳糖苷酶，用於治療法布瑞氏症

**Dominique P. Germain**

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Fabry disease a rare X-linked genetic disorder, results from pathogenic variants in the *GLA* gene, leading to deficient lysosomal α-galactosidase A enzyme activity and multi-organ manifestations. Since 2001, enzyme replacement therapy (ERT), using agalsidase alfa or beta, has been the mainstay treatment, albeit with limitations such as rapid clearance and immunogenicity. Pegunigalsidase alfa, a novel PEGylated recombinant alpha-galactosidase, offers promise as an alternative. Produced in plant cells, pegunigalsidase alfa exhibits enhanced stability, prolonged half-life, and reduced immunogenicity due to pegylation. A phase 1/2 clinical trial followed by an extension study up to 60 months showed Gb3 clearance from renal capillary endothelial cells and notable outcomes in renal function preservation. Three phase 3 clinical trials (BRIDGE, BRIGHT, and BALANCE) have shown favorable efficacy and safety profile, particularly in patients with deteriorating renal function, although caution is warranted in interpreting the results of the BRIDGE and BRIGHT studies which lacked control groups. The BALANCE study, a pivotal phase 3 trial comparing pegunigalsidase alfa with agalsidase beta, revealed in an intention-to-treat analysis of the eGFR decline over 2 years, that the intergroup difference [95%CI] in the median slope was -0.36 mL/min/1.73 m2/year [-2.44; 1.73]. The confidence interval had a lower limit above the prespecified value of -3 mL/min/1.73 m2/year and included zero (indicating that the intergroup difference was not significant). Despite challenges such as IgE-mediated hypersensitivity reactions and immune-complex-mediated glomerulonephritis, pegunigalsidase alfa's approval by the European Medicines Agency and Food and Drug Administration represents a significant addition to Fabry disease therapeutic landscape providing an option for patients in whom the *GLA* variant is not amenable to chaperone therapy or ERT with agalsidase alfa or agalsidase is poorly tolerated or poorly effective.

# Early detection of irreversible cellular damage in cardiac biopsies of Fabry disease before the Formation of Gb3 inclusion bodies

# 法布瑞氏症心臟切片中不可逆轉細胞損傷的早期檢測：Gb3 包涵體形成前的觀察

**Chung-Lin Lee, Dau-Ming Niu**

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Fabry disease (FD) is a lysosomal storage disorder that affects multiple organs, including the heart. The typical pathological hallmark of FD is the presence of globotriaosylceramide (Gb3) inclusion bodies in affected cells. However, the question remains whether significant cellular stress and irreversible damage occur before the formation of these inclusion bodies.

To address this question, we investigated early-stage Gb3 accumulation in fibroblasts from FD patients and myocardial biopsies from G3Stg/GLAko mice and FD patients. Importantly, all biopsies showed detectable Gb3 accumulation under immunofluorescent (IF) staining but lacked the typical FD pathology of Gb3 inclusion bodies. We used IF staining and Western blotting to assess markers of inflammatory and oxidative stress, including interleukin-18 (IL-18), p42/44 mitogen-activated protein kinase (MAPK), and inducible nitric oxide synthase (iNOS). Additionally, we performed IF staining for alpha-smooth muscle actin (α-SMA) to detect the presence of myofibroblasts, which are indicative of fibrosis.

Our results showed that fibroblasts from FD patients, as well as cardiomyocytes from both G3Stg/GLAko mice and FD patients, exhibited significant accumulation of inflammatory markers such as IL-18 and p42/44 MAPK, and the oxidative stress marker iNOS. Furthermore, despite the absence of typical FD pathology, we confirmed the presence of fibrosis in myocardial biopsies from these patients through strong positive staining of α-SMA.

These findings suggest that significant cellular stress and even irreversible damage may occur in the cardiomyocytes of FD patients before the onset of typical pathological changes. This highlights the importance of early intervention in FD patients to prevent irreversible damage and improve their prognosis. Based on our results, we propose that treatment should be initiated much earlier than currently recommended to optimize patient outcomes.

In conclusion, our study provides new insights into the early pathogenesis of FD in the heart and underscores the need for early detection and intervention to prevent irreversible cellular damage. These findings have important implications for the management of FD patients and may guide future research and treatment strategies.

# Newborn screening and treatment of lysosomal storage diseases in Japan

## 日本溶酶體儲積症的新生兒篩檢及治療現況

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Management of inborn errors of metabolism is changing from diet therapy and supportive therapy to enzymes and coenzymes replacement, removal of harmful substances, cell and organ transplantation, and gene therapy. In order to effectively perform these treatments, it is important to diagnose inborn errors of metabolism, which is a rare disease, at an early stage. Also, it is necessary to predict severity and prognosis to optimize the treatment. Neonatal screening is effective for the early diagnosis of inborn errors of metabolism. In recent years, the diseases to be found from the neonatal screen have expanded due to an increase in treatable diseases. Tandem mass screening and screening for lysosome disease are good examples. Genetic analysis is indispensable for these definitive diagnoses. As a result of genetic analysis, it is possible to predict the onset time and complications, and begin the necessary treatment at the optimal period. However, confirmed diagnosis by genetic analysis has restrictions in terms of cost, time, and efficiency, and ethical consideration is also required. It is important to carry out genetic analysis while conducting genetic counseling as necessary. Also, in treatment, transplantation therapy and gene therapy become possible, and the importance of genetic knowledge is even higher. I will introduce new diagnosis and treatment of inborn errors of metabolism available in Japan and importance of understanding of genetic background.

# Update on diagnosis, enzyme replacement therapy for Pompe disease and gene replacement therapy for spinal muscular atrophy in Vietnamese patients

# 越南龐貝氏症診斷、酵素替代療法以及脊髓肌肉萎縮症的基因替代療法的最新進展

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The population in Vietnam was reported 100.3 million inhabitants and number of births was about 1.042 million as of 2023. The rare disease service was set up at the Northern referral center of Pediatrics – Vietnam National Children's Hospital (NCH), Hanoi officially. The NCH in Ha Noi provides services to the population of north Vietnam (~30 million people) for common conditions in children and for rare genetic diseases in whole country. The diagnostic, referral and management workflow for children with neuromuscular disorders including Pompe disease (PD) and spinal muscular atrophy (SMA) is evolving, particularly as newborn screening programs are expanding in tandem with novel therapeutic developments such as enzyme replacement therapy (ERT) and gene therapy.

PD is a rare genetic disorder with an autosomal recessive inheritance pattern and a metabolic consequence. PD birth prevalence is 1:18,711 births (5.3 per 100,000 births) in the dataset of over 11.6M newborns screened for Pompe across 22 states and 8 countries on 4 continents between 2010 and 2022. SMA is caused by a loss or mutation in the survival motor neuron 1 gene (SMN1) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. SMA is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births and carriers is 1:50 in the population. The first children with SMA and PD were confirmed in Vietnam in 2002 and 2015, respectively. The accumulated number of children with PD was 130 cases from 2015 to 2023 at the NCH and six other general/children's hospitals of the country. The number of children with SMA is 791 cases from 2002 to 2022 at NCH. Newborn screening for 6 lysosomal storage diseases including PD was started at NCH in 2021.

The aim of this report is to highlight the database of PD in Vietnam including distribution of subtypes, phenotype, genotype characteristics, mobility, mortality and outcome of ERT. We also mention on database of SMA including distribution of subtypes, mobility, mortality, natural history, complications, efficacy and safety of intravenous infusion of gene replacement therapy, follow up for 32 cases who are less than 2 years of age) as well as clinical trial of intrathecal gene replacement therapy for SMA cases who are ≥ 2 to < 18 years of age.

# Global advancements in newborn genomic screening

# 新生兒基因組篩檢的全球進展

**Nicolas Encina**

*International Consortium on Newborn Sequencing (ICoNS)*

*新生兒基因定序國際聯盟*

Newborn sequencing (NBSeq) has the potential to offer a lifetime of personalized health care and disease prevention that is specific to each individual genome. When fully realized, NBSeq will mark a disruptive transition into personalized medicine and public health. We established the International Consortium on Newborn Sequencing (ICoNS) in 2022 as the first organization specifically dedicated to communicating and sharing progress and best practices in the implementation of NBSeq. Since its inception with principal investigators from 8 separate groups, ICoNS has grown to hundreds of NBSeq specialists, dozens of global projects and is represented by membership from over 40 countries.

The ICoNS mission is to inform the clinical and public health research and implementation of genomic screening in newborns through the harmonization and aggregation of scientific evidence and resources. In that pursuit, ICoNS has commissioned member-run subcommittees that seek to advance the field in precompetitive areas that benefit the community. A few noteworthy subcommittees are: (1) Gene List Subcommittee (2) Data Sharing Subcommittee, and (3) Policy Subcommittee, with others under review.

ICoNS presents an opportunity to gather multi-disciplinary governmental, academic and industry stakeholders and experts from around the world in order to accelerate and harmonize research progress and real-world implementation in NBSeq. The consortium holds an annual conference in October, with the 2024 event scheduled for October 9-10 in New York City, USA. For more information, go to www.iconseq.org.

# Applications of a rapid real time analysis system for whole genome / exome sequencing to clinicians

# 全基因體 / 全外顯子定序即時分析系統在臨床上的應用

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Precision medicine employs genetic testing to accurately predict, prevent, diagnose, and treat diseases. Genetic testing enhances the precision of medication therapies and identifies individuals at higher risk of cancer, even in the absence of symptoms. The decoding of the human genome and advancements in next-generation sequencing technology have made whole genome sequencing (WGS) and whole exome sequencing (WES) more accessible as routine genetic tests in clinical settings.

As we enter the era of preventive medicine, genetic testing provides individuals with a comprehensive understanding of their physiological state, enabling proactive management of health risks based on test results. WGS can identify genetic variations underlying rare and undiagnosed genetic disorders by analyzing the entire genome. Additionally, WGS reveals genetic variations that influence individual responses to medications, allowing personalized drug selection and dosing for optimal therapeutic efficacy and reduced adverse reactions. It can also be used for carrier screening of genetic diseases, informing reproductive planning and aiding in the prevention of transmitting genetic disorders to offspring. However, processing and analyzing the substantial volume of data generated by these tests poses significant challenges. To address this, we collaborated with a bioinformatics service company to develop a "rapid real-time WES/WGS analysis system" that integrates gene analysis technology, cloud computing, big data, and artificial intelligence. This system expedites and ensures accurate diagnoses for patients with genetic diseases, featuring a user-friendly interface and encompassing diverse analyses, including pharmacogenomics, constitutional analysis, proactive analysis, and HLA typing analysis, among others. Furthermore, the system incorporates a genomic AI analysis system (Strata Finder) for assessing the risk of complex diseases, accurately predicting conditions like asthma, acute myocardial infarction (AMI), and stroke with a 99% or higher accuracy rate.

By promoting precision medicine in Taiwan, the system aims to actualize the principle of "prevention is better than treatment" in public healthcare. As technology continues to advance and costs decrease, the clinical applications of WGS are expected to expand further in the future.

# Comprehensive analysis of whole cancer genome

# 癌症基因體的全面分析

**Jan-Gowth Chang**

**張建國**

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*花蓮慈濟醫院 顧問*

Cancer is a complex and heterogeneous disease, which affects nearly all organ systems in human body. Both genetic and non-genetic factors contribute to cancer initiation and progression. The pathophysiology of cancer has made huge progress in recent years due to analyze the results of cancer genomes from many large scale sequencing projects, especially the projects of The Cancer Genome Atlas (TCGA) and the ICGC/TCGA Pan-Cancer Analysis of Whole Genomes (PCAWG). These progresses have a marked impact on the cancer drug development and therapeutic approaches for cancer patients, and they are the key of precision oncology. Now, we treat the cancer patients according to the alterations of their cancer genomes, and the core of drug development is to target these alterations. Recently, Taiwan's government also put more efforts for the clinical use of these fields, and will give an imbursement for cancer genome tests in addition to targeted therapy.

Cancer is difficult to cure for the patient with metastatic disease. Many strategies have been used to treat these patients, and the results are always disappointing, and it is an unmet need for cancer patients. Traditional Chinese Medicine (TCM) has been used for the treatment of many types of diseases including cancer, and many evidences have shown to be a new approach for the cancer therapy. In this talk, I will provide a new proposal of cancer treatment based on the integration of TCM and Western Medicine after comprehensive analysis of cancer genome, and databases from TCGA and TCM.

# Pompe disease : Now and future

# 龐貝氏症的現在與未來

**Chia-Feng Yang**
**楊佳鳳**
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Starting enzyme replacement therapy (ERT) before severe irreversible muscular damage occurs is important in infantile-onset Pompe disease (IOPD). This long-term follow-up study demonstrates our diagnostic and treatment strategies for IOPD and compares our clinical outcomes with those of other medical centers. Out of 1,228,539 infants screened between 1 January 2010 and 28 February 2021, 33 newborns were diagnosed with IOPD in Taipei Veterans General Hospital. Twenty-six patients received regular treatment and monitoring at Taipei Veterans General Hospital.

Echocardiographic parameters, biomarkers, IgG antibodies against alglucosidase alpha, pulmonary function variables, and developmental status were all assessed regularly over an average follow-up duration of 6.18±3.14 years. We compared the long-term treatment outcomes of our patients with those of other research groups. The average age at initiation of ERT in patients with classic IOPD was 9.75±3.17 days. The average of the latest antialglucosidase alpha IgG titre was 669.23±1159.23. All enrolled patients had normal heart sizes, motor milestones, cognitive function and pulmonary function that were near-normal to normal. Compared with patients in other studies, our patients had better outcomes in all aspects. Very early ERT using our rapid diagnosis and treatment strategy allows our IOPD patients to have better outcomes than patients at other medical centers.

Eighteen years later, a new generation of intravenous enzyme replacement therapy (ERT), Nexviazyme, was launched. The efficacy of Nexviazyme in treating Pompe disease was validated in Comet-study involving 100 patients, randomized to receive either Nexviazyme or another FDA-approved enzyme replacement therapy for Pompe disease, Myozyme. On January 21, 2022, the Taiwan Food and Drug Administration added it as an option for Pomope disease, and it will be included in health insurance benefits from April 2023.

All current IOPD and LOPD (late-onset Pompe disease) patients under treatment at our hospital have been successfully switched to Nexviazyme for ERT from Aug 2023. The study aims to analyze patients with Pompe disease treated with this new ERT drug, comparing clinical performance metrics during treatment with Myozyme and after switching to Nexviazyme.

# Newborn screening programs for mucopolysaccharidoses Types I, II, IVA, and VI in Taiwan and the application of gene variants

# 臺灣的黏多醣症第一、二、四A、六型新生兒篩檢計畫與基因變異之應用

**Hsiang-Yu Lin, Shuan-Pei Lin**

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**Background:**Mucopolysaccharidoses (MPSs) are lysosomal storage diseases caused by genetic defects that result in deficiency of one specific enzyme activity, consequently impairing the stepwise degradation of glycosaminoglycans (GAGs). Except for MPS II, the other types of MPS have autosomal recessive inheritance in which two copies of an abnormal allele must be present in order for the disease to develop.

**Methods:**The nationwide newborn screening programs for MPSs were implemented in August 2015, and as of March 2024. 778,341, 667,447, 291,790, and 527,031 newborns have been screened for MPS I, II, IVA, and VI, respectively. A total of 372 suspected infants, including 12 MPS I, 254 MPS II, 106 MPS IVA, and 21 MPS VI, who were referred for MPS confirmation from newborn screening centers in Taiwan, were enrolled. The confirmatory methods used in this study included Sanger sequencing, next-generation sequencing, leukocyte enzyme fluorometric assay, and GAG-derived disaccharides in urine using tandem mass spectrometry assays.

**Results:**Six, twelve, and 10 infants were diagnosed with MPS I, II, and IVA, respectively. The incidences of MPS I, II and IVA were estimated to be 0.77, 1.80 (3.46 in male), and 3.43/100,000 live births, respectively. Two MPS I, six MPS II, and five MPS IVA had received enzyme replacement therapy, including three MPS II also received hematopoietic stem cell transplantation. We investigated 113 gene variants from infants identified through the newborn screening programs for MPS I, II, IVA, and VI in Taiwan, of which 40 were classified as being pathogenic, 40 as likely pathogenic, 23 as uncertain significance, and 10 as benign, according to the guidelines published by the American College of Medical Genetics and Genomics (ACMG). We also present data including biochemical and molecular DNA analyses, and in vitro gene expression analysis using a COS-7 cell transfection experiment, to define the effect of a variant on the disease itself. The severity of MPS is closely related to variation pattern, i.e., missense, nonsense, small deletion, inversion, splicing, and silent mutations.

**Conclusions:**A greater understanding of the genotype-phenotype correlations can help predict the severity and prognosis of individual MPS types correctly, and also prompt intensive and long-term follow-up to monitor the health conditions of highly suspected infants.

# Spinal muscular atrophy: Now and future

## 脊髓性肌肉萎縮症的現在與未來

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Spinal muscular atrophy (SMA) is the most common fatal autosomal recessive disorder, with an estimated incidence of 1 in 10,000 live births. The disease is caused by the absence of a fully functional motor neurone protein gene that produces the survival motor neurone (SMN) protein. SMN protein encoded by two SMN genes: the SMN1 gene, which is the SMA-determining gene, and the SMN2 gene. Patient with SMA was observed due to the absence of the SMN protein, mostly due to deletion or mutation of SMN1.

Since SMA screening of our hospital started from August 2017 at Taipei Institute of Pathology and Chinese Foundation of Health, several individuals with suspected SMA were found. With newborn screening, we can have the opportunity to get the first symptoms of these patients under the regular and closed monitoring plan. Early treatment could be obtained when the children have symptoms. Spinraza®, the first FDA-approved therapy for SMA, is a treatment that targets the SMN2 gene. Spinraza® is an antisense oligonucleotide approved for all ages and types of SMA. Antisense drugs are small snippets of synthetic genetic material that bind to ribonucleic acid (RNA), so they can be used to fix the splicing of genes like SMN2. A gene therapy called “Zolgensma®” has been approved by the U.S. Food and Drug Administration (FDA) for infants under two years of age with all types of SMA. It is a one-time intravenous (IV) infusion. Evrysdi®, an FDA-approved therapy for the treatment of SMA in all ages and all types, is another treatment that works by correcting the splicing of SMN2. Evrysdi® is a small molecule that is taken daily by mouth or by g-tube.

Several children with SMA have received individual therapy at our hospital. The closed and regular monitoring plan leads to early treatment and excellent outcomes. With the long term prognosis and outcome, the current treatment strategy, multidisciplinary teamwork, and further treatment show important. In this section, we will discuss about the now and the future of patients with spinal muscular atrophy.

# Duchenne muscular dystrophy: Now and future

# 裘馨氏症的現在與未來

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Duchenne muscular dystrophy (DMD) is an X-linked debilitating muscular disorder caused by mutations in the dystrophin gene, resulting in muscle fiber necrosis with progressive replacement by fats and fibrotic tissue. Affected boys may have delayed motor milestones and develop progressive muscle weakness. Currently, there is no curative treatment for DMD and glucocorticoids, primarily prednisolone and deflazacort, are the only medications that are shown to slow the decline in muscle strength and improve function in DMD. When DMD is left untreated, patients with DMD inevitably develop loss of mobility, respiratory and cardiac deterioration in consequence of dystrophic changes of muscle.

In addition to motor and cardiac symptoms, cognitive impairment of varying degree is also common in DMD patients. Considering the multi-organ involvement with variable phenotype, the importance of standardized multidisciplinary care for DMD has been highlighted. Over the years, we have conducted multidisciplinary care for DMD patients to hold back the disease progression, to preventively lessen risk of sequelae, to delay pulmonary and other organ decline, and to improve quality of life of patients.

Although there is no cure other than glucocorticoids that can slow down the deterioration, several potential therapies are under investigation, including exon-skipping strategies, stop codon read-through, gene addition or editing therapy, etc. It is unlikely that any of them when used in isolation will be able to halt or reverse the pathological process of DMD although these therapies are expected to slow disease progression. Effective treatment for DMD is likely to require combinations of therapies that address both the primary defect and its secondary consequences. Although these innovative treatments show potential, the future will likely bring more challenges that will demand more efforts.