Postprint of an Exploratory Study on Newborn Screening for Multiple Inherited Metabolic Diseases in Hainan Province

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Abstract

Background The prevalence of inherited metabolic diseases in newborns in China exceeds 0.5%. This study represents the first comprehensive newborn screening for inherited metabolic diseases conducted across the entire Hainan Province, contributing to the prevention and control of birth defects in Hainan and providing laboratory testing methodologies for the diagnosis of inherited metabolic diseases. Objective To investigate the incidence of various inherited metabolic diseases in newborns in Hainan Province and to provide reliable methods and reference basis for the prevention and control of birth defects in Hainan. Methods Using dried blood spots from heel pricks of newborns born in various midwifery medical institutions in Hainan Province from February to December 2024 as samples, screening was performed using tandem mass spectrometry, and reference ranges for relevant detection indicators were calculated using the percentile method. Suspected samples were recalled for diagnostic verification using gas chromatography-mass spectrometry and sequencing. Results A total of 84,184 dried blood spot samples from newborn heel pricks were collected. Using the percentile method, reference ranges for 14 amino acids, 36 carnitines, 1 ketone, 2 adenosines, and 4 lysophosphatidylcholines were calculated from 29,676 samples for newborns in Hainan Province. Thirty-eight cases of various inherited metabolic diseases were diagnosed in newborns, with an incidence rate of 1/2,215 (38/84,184). Twelve diseases were confirmed: phenylketonuria (PKU), hypermethioninemia (HMet), maple syrup urine disease (MUSD), citrin deficiency (CD), primary carnitine deficiency (PCD), short-chain acyl-CoA dehydrogenase deficiency (SCADD), carnitine palmitoyltransferase I deficiency (CPT I), carnitine-acylcarnitine translocase deficiency (CACT), 3-methylcrotonyl-CoA carboxylase deficiency (MCCD), glutaric acidemia type I (GA-I), glutaric acidemia type II (GA-II), and 2-methylbutyrylglycinuria (SBCADD), with incidence rates ranging from 1/84,184 to 1/6,475, showing considerable variation. The three most frequently detected diseases were PCD (13 cases), SCADD (6 cases), and CD

(5 cases). A total of 42 mutations across 12 genes were identified. Conclusion This study established for the first time the normal reference ranges for newborn screening of various inherited metabolic diseases in Hainan Province, providing evaluation indicators for subsequent screening. Following the implementation of comprehensive free screening, it was determined for the first time that the incidence of various inherited metabolic diseases in newborns in Hainan Province is relatively high, with complex and diverse genetic variations, particularly fatty acid oxidation disorders such as PCD, SCADD, and CD being more common. Newborn screening for various inherited metabolic diseases is of significant importance for birth defect prevention and control in Hainan.

Full Text

Preamble

Exploratory Study on Screening of Multiple Inherited Metabolic Disorders in Newborns in Hainan Province

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Abstract
Background: The prevalence of neonatal inherited metabolic disorders exceeds 0.5% in China. This study represents the first comprehensive population-wide screening for these conditions across Hainan Province, contributing to regional birth defect prevention and establishing diagnostic laboratory capabilities for inherited metabolic diseases.
Objective: To investigate the incidence of multiple inherited metabolic disorders (IMDs) among newborns in Hainan Province and provide reliable methods and reference data to support birth defect prevention and control efforts.
Methods: Dried blood spot (DBS) samples were collected from heel pricks of newborns born between February and December 2024 at all obstetric healthcare facilities in Hainan Province. Screening was performed using tandem mass spectrometry, with reference ranges for relevant biomarkers established using the percentile method. Suspected cases were recalled for confirmatory diagnosis via gas chromatography-mass spectrometry (GC-MS) and gene sequencing.
Results: A total of 84,184 DBS samples were collected. Using the percentile method, reference ranges were established for 14 amino acids, 36 acylcarnitines, 1 ketone, 2 adenosines, and 4 lysophosphatidylcholines based on 29,676 samples, providing the first normative reference data for Hainan Province. Thirty-eight cases of IMDs were diagnosed, yielding an incidence rate of 1/2,215 (38/84,184). Twelve distinct diseases were confirmed: phenylketonuria (PKU), hypermethion-

inemia (HMet), maple syrup urine disease (MSUD), citrin deficiency (CD), primary carnitine deficiency (PCD), short-chain acyl-CoA dehydrogenase deficiency (SCADD), carnitine palmitoyltransferase I deficiency (CPT I), carnitine-acylcarnitine translocase deficiency (CACT), 3-methylcrotonyl-CoA carboxylase deficiency (MCCD), glutaric acidemia type I (GA-I), glutaric acidemia type II (GA-II), and short/branched-chain acyl-CoA dehydrogenase deficiency (SBCADD), with incidence rates ranging from 1/84,184 to 1/6,475. The three most prevalent disorders were PCD (13 cases), SCADD (6 cases), and CD (5 cases). A total of 42 mutation sites across 12 genes were identified.

Conclusion: This study establishes the first reference ranges for newborn IMD screening in Hainan Province, providing critical diagnostic criteria for subsequent screening programs. Following implementation of universal free screening, the data reveal a relatively high incidence of IMDs among Hainan newborns, with notable genetic complexity and diversity. Disorders of fatty acid metabolism—particularly PCD, SCADD, and CD—were most frequently detected. These findings underscore the importance of expanded newborn IMD screening for birth defect prevention and control in Hainan Province.

[**Key words**] Neonatal screening; Inherited metabolic disorders; Dried blood spots; Incidence rate; Newborn screening; Hainan Province

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Introduction

Inherited metabolic disorders in newborns, also known as inborn errors of metabolism (IEM), represent a broad category of diseases characterized by abnormal metabolic biochemical markers. These disorders seriously compromise population health quality and constitute a subset of monogenic diseases. The vast majority of IEMs follow autosomal recessive inheritance, though some exhibit autosomal dominant, X-linked, or mitochondrial inheritance patterns. These conditions encompass various metabolic abnormalities, including disorders of amino acid metabolism, organic acid metabolism, urea cycle, fatty acid oxidation, and carbohydrate metabolism. While individual IEMs have an incidence below 1/10,000, the collective prevalence is substantial, with reports indicating that newborn morbidity exceeds 0.5%. Consequently, multi-disease IEM screening in newborn populations represents a critical task for birth defect prevention worldwide, with tandem mass spectrometry-based screening already implemented in several countries.

According to China' s "Management Measures for Newborn Disease Screening" (Former Ministry of Health Order No. 64), provincial health administrative departments may expand screening diseases based on local medical resources, population needs, and disease incidence. Although Hainan Province initiated tandem mass spectrometry screening in 2016, screening coverage remained below 10% of the provincial birth population until January 2024. The increasing number of detected IEM cases—19/37,482 in Hainan' s ethnic minority regions and 88/185,660 in Haikou—prompted provincial government attention. Following the issuance of the "2024 Hainan Province Free Newborn Multiple Inherited Metabolic Disease Screening Program Implementation Plan" (Qiongwei Maternal and Child Health Letter [2024]), universal free screening was achieved for the first time under the principle of "screen all who should be screened." This study reports data from the 2024 screening program to comprehensively understand the epidemiology of IMDs in Hainan and provide reliable methods and reference data for birth defect prevention and control.

Methods

1.1 Study Population

Newborns delivered at obstetric institutions across Hainan Province between February 1 and December 31, 2024, were enrolled in this study. Following informed consent and signing of the "Hainan Province Newborn Inherited Metabolic Disease Screening Consent Form," heel-prick blood samples were collected from neonates at 48 hours of age to prepare dried blood spot samples for free tandem mass spectrometry IEM screening, in accordance with the "Expert Consensus on Collection, Delivery, and Preservation of Newborn Disease Screening Filter Paper Blood Spots." A total of 84,184 newborn DBS samples were collected. This study was approved by the Medical Ethics Committee of Hainan Women and Children' s Medical Center [Approval No.: HNWCMC Ethics Review 2024 (55)].

1.2 Sample Collection

DBS samples were prepared following the "Expert Consensus on Collection, Delivery, and Preservation of Newborn Disease Screening Filter Paper Blood Spots."According to the "Technical Specifications for Newborn Disease Screening Blood Spot Collection," screening cards must be completely filled out with four blood spots $ $8 mm in diameter, uniformly penetrated on both sides, without duplicate blood drops, and air-dried naturally.

1.3 Instruments and Reagents

The following equipment and reagents were used: 2081Panthera-Puncher™9 puncher (Finland PerkinElmer, 3 mm punch diameter), QSight225MD tandem

mass spectrometer (Jiangsu Xinbo Biotech), Agilent7890B-5977A GC-MS (Agilent Technologies, USA), BS-2000M biochemical analyzer (Mindray, China), MicBio-IV incubator shaker (Aibensen, China), XW-80A mixer (Haimen Qilin Bell, China), KQ-100 ultrasonic cleaner (Kunshan Ultrasonic Instruments), ABI3730xl sequencer (Applied Biosystems). Reagents included: NeoBase™2 non-derivatized amino acids, acylcarnitines, adenosines, lysophosphatidylcholines, and succinylacetone assay kit (Xinbo Biotech, tandem mass spectrometry), urinary organic acids kit (Biosen Biotech), creatinine assay kit (Beijing Beijian Xinchuangyuan Biotech), QIAamp whole blood DNA extraction kit (Qiagen, Germany), NEBNext DNA library preparation kit for Illumina (Beijing Maijino), and whole exome capture kit (Beijing Maijino).

1.4 Screening and Diagnostic Procedures

1.4.1 Tandem Mass Spectrometry Screening and Clinical Interpretation The NeoBase™2 kit was used to detect 14 amino acids, 36 acylcarnitines, 1 ketone, 2 adenosines, and 4 lysophosphatidylcholines in newborn DBS samples. From February to May 2024, manufacturer reference ranges were used. After accumulating 29,676 valid screening data points, laboratory-specific reference ranges were calculated using the percentile method and implemented from June to December 2024. Tandem mass spectrometry data were analyzed by clinical physicians, who issued recommendations and uploaded reports to the "Hainan Maternal and Child Health System Platform" for network distribution. Suspected IEM cases were recalled for subsequent verification and diagnosis.

1.4.2 Urinary Organic Acid Analysis and Clinical Interpretation Newborns with suspected IEMs recommended for urinary organic acid analysis underwent GC-MS testing. Clinical physicians analyzed the results and issued reports.

1.4.3 Gene Sequencing and Clinical Interpretation Two milliliters of peripheral blood were collected from suspected IEM neonates and their parents. DNA was extracted, fragmented via ultrasonication, and libraries were constructed. Whole exome capture was performed using capture kits, followed by paired-end sequencing on a next-generation sequencer. Molecular diagnostic center physicians reviewed the genetic data and issued reports.

1.5 Clinical Diagnosis of IEMs

Clinical diagnosis was made by the Hainan Newborn Screening Center clinical team based on tandem mass spectrometry data, urinary organic acid analysis, and/or genetic analysis reports.

1.6 Cutoff Value Calculation and Statistical Methods

SPSS 13.0 statistical software was used. Following the "Expert Consensus on Tandem Mass Spectrometry Technology for Newborn Disease Screening"and "Expert Consensus on Establishing Cutoff Values for Newborn Genetic Metabolic Disease Screening Indicators," the percentile method was applied to normal newborns (excluding low birth weight, preterm, and post-term infants that affect metabolite levels). Based on reported disease incidence and clinical significance of each indicator, the 1st percentile (P1.0) and 99th percentile (P99.0), 0.5th percentile (P0.5) and 99.5th percentile (P99.5), and 0.1th percentile (P0.1) and 99.9th percentile (P99.9) were calculated. After rounding, preliminary reference range limits were established. New reference ranges were discussed with clinicians and documented before clinical use. Count data were expressed as relative numbers, with $P<0.05$ considered statistically significant.

Results

2.1 Incidence of Multiple IEMs in Hainan Newborns

The incidence of multiple IEMs among Hainan newborns was 1/2,215 (38/84,184). Reference ranges for 14 amino acids, 36 acylcarnitines, 1 ketone, 2 adenosines, and 4 lysophosphatidylcholines were established. From February to May 2024, 29,676 valid data points were collected, with 984 initial positive screens (3.29% positivity rate), 748 recalls (76.02% recall rate), and 11 final IEM diagnoses. From June to December 2024, 54,302 samples were collected: 1,879 initial positive screens (3.40% positivity rate), 1,716 recalls (91.33% recall rate), and 27 final IEM diagnoses (Table 1 , Table 2).

Comparison between manufacturer reference ranges and newly calculated ranges showed no significant differences in initial screening positivity rates (^{2}=1.643, P=0.200) or IEM diagnosis rates (^{2}=0.712, P=0.399). However, the positive predictive value of the new reference range (1.57%) was higher than that of the manufacturer range (1.47%) (Table 2).

2.2 Distribution of IEM Diseases in Hainan Newborns

This study diagnosed 38 cases of IEMs in Hainan newborns, with fatty acid metabolism disorders being most common, followed by organic acid metabolism disorders (Table 3). The breakdown was as follows: (1) Amino acid metabolism disorders: 4 cases including 2 phenylketonuria (PKU), 1 maple syrup urine disease (MSUD), and 1 hypermethioninemia (HMet); urea cycle disorders: 5 cases. (2) Five cases of citrin deficiency (CD). (3) Organic acid metabolism disorders: 7 cases including 2 cases of 3-methylcrotonyl-CoA carboxylase deficiency (MCCD), 2 cases of glutaric acidemia type I (GA-I), and 3 cases of 2-methylbutyrylglycinuria (SBCADD). (4) Fatty acid metabolism disorders: 22 cases including 13 primary carnitine deficiency (PCD), 6 short-chain acyl-CoA

dehydrogenase deficiency (SCADD), 1 carnitine palmitoyltransferase I deficiency (CPT I), 1 carnitine-acylcarnitine translocase deficiency (CACT), and 1 glutaric acidemia type II (GA-II). Among these diseases, PCD, CD, and SBCADD were the most common single-disease entities in Hainan.

Discussion

The universal free screening program rapidly achieved 100% coverage with a participation rate of 99.63%. Following the technical and methodological expert consensus guidelines, 29,676 valid data points were collected from February to May 2024 to establish the first reference ranges for amino acids, acylcarnitines, succinylacetone, adenosines, and lysophosphatidylcholines in Hainan newborns. Comparison of screening outcomes using manufacturer versus locally calculated reference ranges demonstrated no statistical differences in positivity or diagnosis rates, validating both approaches. However, the locally calculated ranges showed slightly higher initial positivity and incidence rates, along with improved positive predictive value (1.57% vs. 1.47%), providing more appropriate criteria for the Hainan population while reducing missed cases. Because the free screening program notice was issued late, February samples represented catch-up screening, resulting in a lower 76.02% recall rate for February-May. Subsequent screening achieved a 91.33% recall rate from June-December.

This first systematic province-wide screening revealed an IEM incidence of 1/2,215 (38/84,184), consistent with international reports ranging from 1/2,555 to 1/784 and higher than the national average of 1/2,585. The three most prevalent disorders were PCD, CD, and SBCADD. Notably, the PCD incidence of 1/6,476 was higher than the 1/10,000 threshold, though lower than the 1/3,740 reported in Hainan' s ethnic minority regions. Further analysis revealed a statistically significant difference between PCD incidence in Li ethnicity newborns (5/11,499) and Han ethnicity newborns (8/70,732) (^{2}=6.477, P=0.011), suggesting the Li population may be predisposed to PCD. This disparity may relate to genetic founder effects from long-term geographic isolation and endogamous practices. This ethnic variation aligns with global patterns, as PCD incidence ranges from 1/250,000 in Egyptians to 1/30 in Faroe Islanders.

Genetic analysis identified nine SLC22A5 mutations, with c.51C>G as a hotspot, differing from the most common Chinese variant (c.1400C>G) and Fujian Quanzhou variant (c.760C>T) but similar to neighboring Guangzhou (c.51C>G). PolyPhen-2 prediction suggests c.51C>G (p.Phe17Leu), though a synonymous mutation, may affect mRNA splicing stability and cause loss of carnitine transporter function. This "regional mutation hotspot" indicates Hainan may be a key node for IEM genetic variation research in East Asia, warranting investigation of potential tropical climate effects on gene selection—for example, whether fatty acid metabolism genes like ACADS accumulate functional mutations due to adaptive evolution in high-temperature

environments.

SCADD cases revealed ACADS gene hotspots at c.322G>A and c.655G>A, differing from hotspots in Lianyungang (c.1031A>G and c.1130C>T) and Hefei (c.1031A>G). Additionally, the SLC25A13 c.852_{855del} mutation accounted for 80% (4/5) of CD cases, differing by only one base from the common Chinese c.851_{854del} but potentially causing more severe protein truncation. Whether such "Hainan-specific" variants result from environment-gene interactions requires functional experimental validation.

Interestingly, two CD cases had initial citrulline values within both manufacturer and locally calculated reference ranges but were later diagnosed after presenting with cholestasis. Subsequent tandem mass spectrometry showed elevated citrulline (64.87 mol/L and 95.50 mol/L), and genetic testing confirmed homozygous c.852_{855del} variants. Literature confirms that only 40% of neonatal cholestasis cases due to citrin deficiency are detectable by tandem mass spectrometry in the neonatal period because low total amino acid levels result in citrulline, phenylalanine, tyrosine, and methionine values that fall below detection thresholds.

The universal free screening program increased participation from 6.85% (5,934/86,585) in 2023 to 100% in 2024, with diagnosed cases increasing nearly 40-fold compared to the self-pay era (3 vs. 38 cases), demonstrating Hainan' s strengthening birth defect prevention system. This study establishes the first genetic and metabolic map of IEMs in Hainan, revealing unique characteristics of inherited metabolic diseases in tropical regions and underscoring the critical importance of expanded newborn screening for birth defect prevention and control.

Author Contributions

ZHAO Zhendong conceptualized the study and designed the research protocol. ZHAO Peizhen and XU Haizhu conducted experiments, implemented the study procedures, selected subjects, and performed laboratory testing and detection. ZHAO Peizhen and XU Haizhu collected, curated, and statistically analyzed the data. ZHAO Peizhen drafted the manuscript. XU Haizhu revised the final version and takes responsibility for the paper.

Conflict of Interest

The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.