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ORIGINAL ARTICLE

# Incidence of severe combined immunodeficiency through newborn screening in a Chinese population

Yin-Hsiu Chien [a,b], Shu-Chuan Chiang [a], Kai-Ling Chang [a], Hsin-Hui Yu [b], Wen-I Lee [c], Li-Ping Tsai [d], Li-Wen Hsu [a], Min-Huei Hu [a], Wuh-Liang Hwu [a,b,*]

[a] *Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan*
[c] *Department of Pediatrics, Chang Gung Memorial Hospital and Children's Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[d] *Department of Pediatrics, Buddhist Tzu Chi General Hospital, Taipei Branch, New Taipei City, Taiwan*

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**KEYWORDS**
newborn screening;
severe combined immunodeficiency disease;
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TRECs

*Background/Purpose:* In order to know the true incidence of severe combined immunodeficiency (SCID) in a Chinese population, we conducted and implemented SCID newborn screening in Taiwan.
*Methods:* Between May 1, 2010 and December 31, 2011, the National Taiwan University Hospital Newborn Screening Center screened all newborns for T-cell lymphopenia by measuring the copy number of T-cell receptor excision circles (TRECs) and RNase P. Newborns with low TREC values were subjected to complete blood cell counts and flow cytometry.
*Results:* A total of 106,391 newborns were screened using the TREC assay over a period of 19 months. Five newborns were immediately referred for confirmatory tests, including two SCID patients and two patients with persistent T-cell lymphopenia; a third SCID patient was found 2 months after the study period. All three SCID cases received stem cell transplantation at the age of 2–5 months. We also identified five cases of 22q11.2 microdeletion syndrome. During this period, two SCID patients from among the unscreened newborns were reported, and they died at ages 3 months and 4 months, respectively.
*Conclusion:* Newborn screening to measure the number of TREC copies successfully identifies newborns with T-cell lymphopenia, 22q11.2 microdeletion syndrome, and other high-risk conditions. Taken together, the incidence of T-cell lymphopenia in apparently healthy newborns is more than 1 in 11,821, and further attention to their immune functions is warranted.
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* Corresponding author. Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan.
*E-mail address:* hwuwlntu@ntu.edu.tw (W.-L. Hwu).

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## Introduction

Severe combined immunodeficiency disease (SCID) is a term that describes a spectrum of primary immunodeficiencies that comprise more than 16 independent genetic conditions,[1,2] all of which result in severe defects in cellular and humoral immunity. Patients with SCID usually present normally at birth but then suffer from life-threatening infections and ultimately die before 1 year of age if not treated appropriately. Hematopoietic stem cell (HSC) transplantation before the onset of serious infections markedly improves the long-term prognosis of these patients.[3,4] With proof that the T-cell receptor excision circle (TREC) assay can detect patients with SCID and other T-cell deficiencies, in conjunction with evidence suggesting that SCID met the criteria for newborn screening, the Federal Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children of the United States recommended in 2010 that SCID be included in the recommended uniform national newborn screening (NBS) panel for infants in all states.

Newborns with immunodeficiency attract special attention in Taiwan. First, most patients (85%) affected by SCID and other combined T-cell and B-cell immunodeficiencies had symptom onset before 1 year of age and high mortality (30%).[5] Second, babies in Taiwan receive Bacille Calmette-Guérin (BCG) vaccination immediately after birth. Two cases of SCID babies who received BCG vaccination at 1 day old have been reported.[5] Additionally, BCG infection occurred in 23.8% of infants with SCID and caused complications in 50% of patients who underwent HSC transplantation.[5] Although the incidence of SCID has been reported to be low,[6] this low incidence probably reflects an underestimation rather than an ethnic difference.[5] In order to know the true incidence of SCID and related T-cell immunodeficiency, we conducted the first SCID NBS in Taiwan and present the results.

## Materials and methods

The SCID pilot screen program was integrated into the regular screening program of the National Taiwan University Hospital (NTUH) Newborn Screening Center, which routinely screens 35—37% of newborns in Taiwan. The unscreened population in Taiwan served as controls. Parental consent was obtained for each newborn to allow the newborn screening card to be used for the TREC assay. The Institutional Review Board (IRB) of the hospital approved this pilot program. The screening is now ongoing on a self-paid base, and is provided to all babies born in Taiwan including those screened by other screening centers.

The TREC assay was performed as previously described[7] with slight modifications, namely the elution volume and the volume for real-time quantitative PCR (RT-PCR). Briefly, one 3.2-mm paper disk was punched from the dried blood spot (DBS) newborn card. DNA was then extracted from the paper disk (by Generation DNA Purif. Solution and Generation DNA Elution Solution, QIAGEN), and RT-qPCR was performed to estimate the values for the TREC assay and RNase P (by TaqMan® Gene Expression Master Mix, Applied Biosystems®). The TREC value was normalized to microliters of whole blood based on the estimation that each 3.2-mm paper disk contains 3 μL of whole blood. The cutoff value for the TREC assay was $<$40 TRECs/μL, as the revised cutoff in the original program.[8] The value for RNase P served as a control for sample integrity and blood quantity. A DBS with a zero TREC value but a normal RNase P value was defined as abnormal. A DBS with a TREC value between zero and 40 was defined as inconclusive. All inconclusive DBSs required a repeat DBS, and either a low or zero TREC value on the repeat DBS was defined as abnormal. Newborns with abnormal SCID screening required a whole blood sampling so that a complete blood count and flow cytometry could be performed to confirm the SCID diagnosis. For a DBS with an abnormal or inconclusive screening result, *TUPLE1* gene copy number analysis for chromosome 22q11.2 microdeletion syndrome[9] was performed.

## Results

### The screening performance

The overall distribution for the number of TRECs per microliter of whole blood extracted from dried blood spots

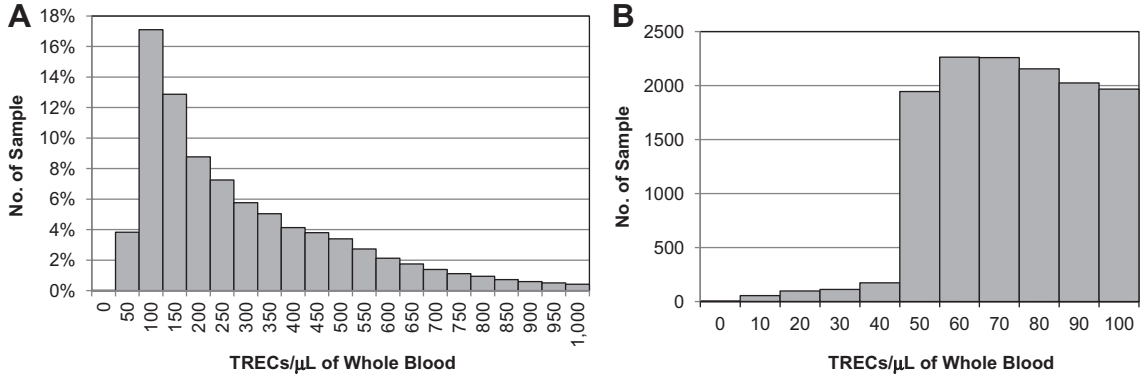


**Figure 1** Distribution of T-cell receptor excision circle (TREC) values in newborns. (A) Overall distribution. (B) Distribution over the low TREC value ranges.

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