Newborn Screening for SCID in Wisconsin

The 2010 Newborn Screening and Genetics Testing Symposium
Orlando, FL May 3-6, 2010

Mei Baker, M.D., FACMG
Assistant Professor, Department of Pediatrics
Science Director, NBS Laboratory at WSLH
University of Wisconsin School of Medicine and Public Health
Newborn Screening for SCID in Wisconsin

- WI SCID pilot program - began in January 2008
- Babies Screened to date: 162,059
- Findings:
  - PID: Rac2 mutation, DiGeorge, Jacobsen's (CVID?)
  - Idiopathic lymphopenia
  - Congenital abnormalities

---

Breaking News!!!

First SCID Baby Identified by NBS
Using Wisconsin TREC assay
Severe Combined Immunodeficiency (SCID)

- Life-threatening Infections in first year of life recurrent and persistent
  All types: bacterial, viral, and fungal severe--including sepsis, meningitis

- Vaccine-Acquired infection

- T cells decreased or absent

- B cells absent or non-functional

- Allogeneic BMT saves life
Does SCID fulfill NBS criteria? ....YES!!

- Prevalence of the disease (1:100,000 or greater)
  - SCID: 1:66,000 (conservative estimate)

- Can the disorder be detected by routine physical exam?
  - SCID: No, SCID baby appears normal at birth.

- Does the disorder have a short asymptomatic period after birth?
  - SCID: Yes, SCID baby can be protected by passive maternal immunity.

- Does the disease cause serious medical complications?
  - SCID: Yes, universally fatal within the first year of life

- Is there potential for successful treatment?
  - SCID: Yes, hematopoietic stem cell transplantation

- Is there a confirmatory test?
  - SCID: Yes, lymphocyte subpopulation analysis (flow cytometry)

- Does early intervention lead to better outcome?
  - SCID: Yes!

- Is there a screening test?
  - SCID: Yes, measurement of TRECs using real-time qPCR
TRECs are reduced in nearly ALL forms of SCID

Genet Med 2004;6(1):16–26. • = T-cell receptor excision circle (TREC)
Unique characteristics of TRECs:

Episomal DNA circles: stable and can be detected by PCR. They do not replicate, so they are diluted out as T cells undergo many divisions.

The δRec-ΨJa TREC is produced by ~70% of all T cells that express α/β T cell receptor
TRECs as a screening marker for SCID

- Measurement of TRECs by real-time PCR can accurately identify infants with SCID using newborn dried blood spots.
  

- It is feasible to conduct high throughput TREC assay for SCID screening in a public health laboratory.
  
  Routes JM, Baker MW, et al. *JAMA* 2009
Overall Analysis Scheme

NBS Card (NSC)
a.k.a. Guthrie Card
Dried blood spots (DBS)

3 mm punch

96 well plate

Extract DNA

Amplify TREC by real-time QPCR

Analyze

TREC plasmid calibrators

ΔRn (amplification)

ABI 7900HT Fast Real-Time PCR System
SCID Screening Algorithm

Request Repeat NBS Card

Sample Entry

TRECs <25

TRECs ≥25

Issue Normal Report

Issue Inconclusive Report

TRECs <25 & low β-actin

TRECs <25 & normal β-actin

Premature

(Follow State NBS Guidelines & Repeat NBS Screen Every 2 Weeks)

 ISSUE ABNORMAL REPORT

Notify PCP

Recommended

Flow Cytometry Evaluation For T cell lymphopenia

Alternative

Repeat NBS Screen TREC assay
What's new?

• Screening cut-off modification

• Automation vs. Manual

• Multiplexing vs. Single tube

• 384 well vs. 96-well
Multiplexing the 96-well plate
Multiplexing the 384-well Plate
Conclusions

- The NBS TREC assay allows for high-throughput, population-based screening for SCID on a state level.

- The NBS TREC assay is relatively inexpensive and highly reproducible.

- The NBS TREC assay has a low screening positive rate.

- The TREC assay successfully identifies infants with SCID and other primary immunodeficiency diseases.
Funding Supports

Jeffrey Modell Foundation
Children's Hospital of Wisconsin Foundation
Wisconsin State Hygiene Laboratory (WSLH)
Center for Disease Control and Prevention
Acknowledgements

CHW/MCW:
Jack Routes, MD
Bill Grossman, MD, PhD.
James Verbsky MD, PhD.
Dennis Schauer, MT

UWSMPH/Pediatrics
Christine Seroogy, MD

DHS
Murray Katcher, MD, Ph.D.

UWSMPH/WSLH:
Ron Laessig, PhD
Charles Brokopp, Dr. PH
Daniel Kurtycz, MD
Gary Hoffman, BS
Michael Cogley, BS
David Mickle, BS

CDC:
Robert Vogt, PhD.
Francis Lee, PhD.

NIAID:
Dr. Daniel Douek: TREC plasmids