# Newborn screening for SCID and related forms of Primary Immunodeficiency



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# Aims

To review the epidemiology and possible presentations of primary immunodeficiency disorders.

To learn about the TREC newborn screening assay, and what to do with a positive result.

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# Speaker Disclosures

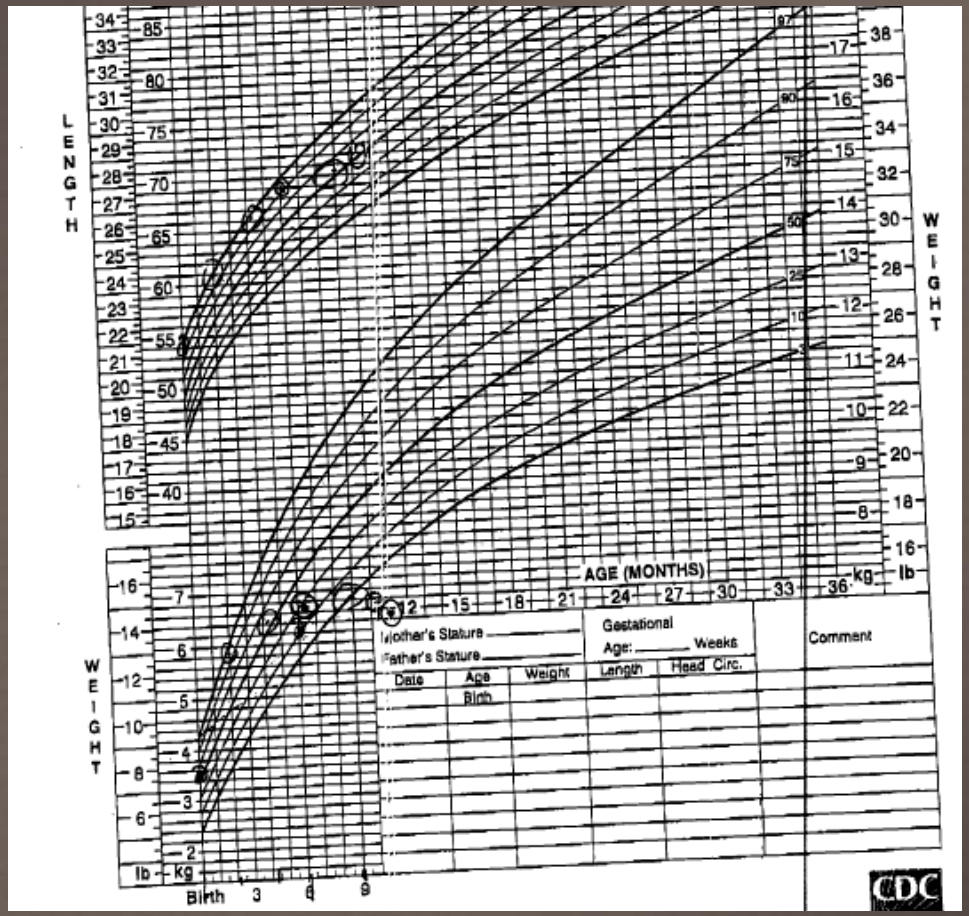
No disclosures to declare.

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# Case: 10 month old girl

Ex FT infant, poor weight and chronic diarrhea since 2 months of age.

No prior known infections, negative FH.




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## Initial workup

CBC:

- WBC: 5.6
- Hb: 11.3
- Hct: 34.1
- MCV: 79.1
- Plt: 386
- ANC: 2055
- ALC: 3102
- Eos: 0.2%
- Monos: 6.9%

CMP:

- Na: 135
- K: 3.9
- Cl: 104
- CO2: 24
- BUN: 4
- Cr: 0.2
- Glu: 70
- Total protein: 4.9
- Albumin: 3.0
- Alk Phos: 126
- ALT: 84
- AST: 87
- Phos: 4.8
- Mg: 2.3
- GGT: 17

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# Differential



- **Primary GI disease**
  - IBD, allergic enterocolitis,
  - GI channelopathy
- **Metabolic disorder** or **CF**
  - Newborn screening catches many but not all
- **Chronic infection**
  - HIV
  - Immune disorder

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## Further testing

- Stool testing: negative for norovirus, enterovirus, parechovirus, adenovirus, O&P, culture
- Negative CMV, EBV PCRs (blood)
- Normal fecal elastase (434)

- **Positive Rotavirus Antigen EIA**

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# Further testing

| Component<br>*Latest Ref Rng* | 12/15/2010 |
|---|---|
| Pneumococcal Serotype 1, IgG<br>*() ug/mL* | 0.08 |
| Pneumococcal Serotype 3, IgG<br>*() ug/mL* | 0.02 |
| Pneumococcal Serotype 4, IgG<br>*() ug/mL* | 0.02 |
| Pneumococcal Serotype 5, IgG<br>*() ug/mL* | 0.64 |
| Pneumococcal Serotype 6B, IgG<br>*() ug/mL* | 0.07 |
| Pneumococcal Serotype 7F, IgG<br>*() ug/mL* | 0.16 |
| Pneumococcal Serotype 8, IgG<br>*() ug/mL* | 0.04 |
| Pneumococcal Serotype 9N, IgG<br>*() ug/mL* | 0.04 |
| Pneumococcal Serotype 9V, IgG<br>*() ug/mL* | 0.06 |
| Pneumococcal Serotype 12F, IgG<br>*() ug/mL* | 0.17 |
| Pneumococcal Serotype 14, IgG<br>*() ug/mL* | 0.04 |
| Pneumococcal Serotype 18C, IgG<br>*() ug/mL* | 0.05 |
| Pneumococcal Serotype 19F, IgG<br>*() ug/mL* | 0.11 |
| Pneumococcal Serotype 23F, IgG<br>*() ug/mL* | 0.04 |
| Anti-Tetanus Antibodies<br>*>0.15 IU/mL* | < 0.01 (*L) |
| Anti-Diphtheria Antibodies<br>*>0.100 IU/mL* | < 0.004 (*L) |
| H Influenzae B Ab, IgG<br>*() ug/mL* | 0.0 |

| Component<br>*Latest Ref Rng* | 12/15/2010 |
|---|---|
| Immunoglobulin A<br>*27 - 169 mg/dL* | 153 |
| Immunoglobulin M<br>*43 - 113 mg/dL* | 43 |
| Immunoglobulin E<br>*0 - 15 IU/mL* | < 4 |
| Immunoglobulin G<br>*383 - 1070 mg/dL* | 66 (*L) |

**Hypogammaglobulinemia**
**No vaccine responses**

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# Further testing

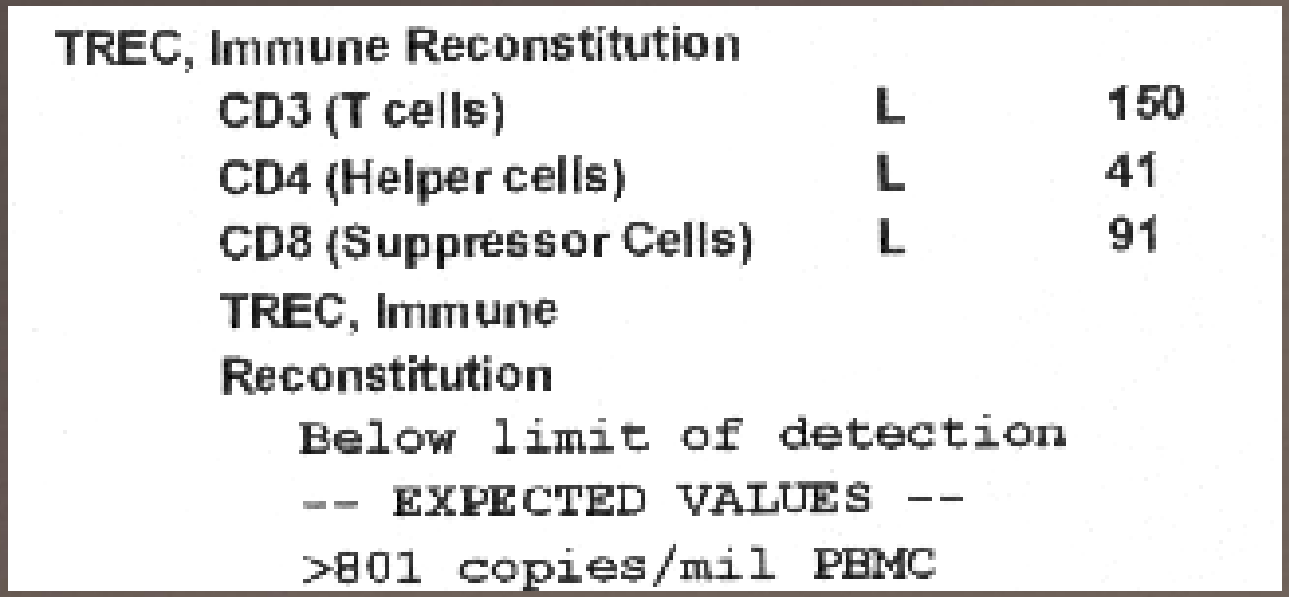
## Lymphocyte Flow Cytometry

| Marker | Value (cells/mcl) | Normal range (cells/mcl) |
|---|---|---|
| CD3+ (T-cells) | 242 | 1600-6700 |
| CD3/CD4+ | 86 | 1000-4600 |
| CD3/CD8+ | 15 | 400-2100 |
| CD4/CD45RA+ | 61 | 500-1100 |
| CD4/CD45RO+ | 57 | 150-600 |
| CD16/56+, CD3- (NK cells) | 223 | 200-1200 |
| CD19+ (B-cells) | 1735 | 600-2700 |

**Profound T-cell Lymphocytopenia**

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# Diagnosis



TREC, Immune Reconstitution

| | | |
|---|---|---|
| CD3 (T cells) | L | 150 |
| CD4 (Helper cells) | L | 41 |
| CD8 (Suppressor Cells) | L | 91 |

TREC, Immune Reconstitution

Below limit of detection

-- EXPECTED VALUES --

>801 copies/mil PBMC

**Dx: Severe combined immunodeficiency**

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# Epidemiology:
# Primary immunodeficiency

Over 200+ known congenital immunologic defects

- In total, primary immunodeficiency is thought to occur as frequent as 1 in 5000.

Comparison: HIV rates in the US

- 0.3% overall (2009 data)
- Only ~15,000 cases under age 13

**In US children, congenital immunodeficiency now is more prevalent than HIV.**

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## Constitutional Red Flags

- Failure to thrive
- Chronic diarrhea
- Severe allergic disease
- Autoimmune phenomena

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# Sentinel Infections

Severe infections with ordinary pathogens

- Deep tissue infections (empyema, meningitis)
- Unusual sites of infection (liver abscess)

- Opportunistic infections
  - Fungal infections
  - Live-vaccine associated illnesses
  - Mycobacteria
  - Parasitic infections (cryptosporidium)
  - CMV

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# 10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. **If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.**

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

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# Severe Combined Immunodeficiency

- Defects in T-cell development or survival
- Present in first year of life:
  - **FTT**
  - **Chronic diarrhea**
  - **Opportunistic infections**: PJP, candida, MAI, vaccine-associated disease, CMV
  - **Prolonged or unusually severe viral illnesses**
  - Rarely **autoimmune phenomena** (Omenn's)

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# SCID Redefined with Newborn Screening

- Incidence 1/58,000 births.
- Typical SCID: <300/uL autologous T cells; <10% of normal PHA response; maternal T cells often present; gene defect.
  - Recurrent infections and weight loss beginning in the first year.
  - Early death unless a working immune system can be established.
- Leaky SCID: Low T cells, no maternal T cells, impaired PHA response; gene defect with partial activity.
  - May present later than typical SCID with autoimmune phenomena, malignancy, or opportunistic infections.

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# The ever-growing list of SCID genes

| Cellular phenotype | | | Gene Defect | Inheritance | % of cases |
|---|---|---|---|---|---|
| T-cells | B-cells | NK cells | | | |
| Low/Absent | Present | Absent | IL2-Rγ (common γ chain) | X-linked | 45-50% |
| Low/Absent | Present | Absent | Janus-associated kinase-3 (JAK3) | AR | 7% |
| Low/Absent | Present | Present | IL7-Rα | AR | 10% |
| Low/Absent | Present | Present | CD3 ε, δ, or ζ subunits | AR | Rare |
| Low/Absent | Present | Present | FOXN1 | AR | Very rare |
| Low/Absent | Present | Present | 22q11 (athymia in complete Digeorge syndrome) | AD | Very rare |
| Low/Absent | Present | Variable | CD45 | AR | Rare |
| Low/Absent | Present | Present | Coronin-1A | AR | Very rare |
| Absent | Absent | Present | RAG1/2 | AR | <5% |
| Absent | Absent | Present | DCLRE1C (Artemis) | AR | <5% |
| Absent | Absent | Present | Cernunnos (XLF) | AR | Very rare |
| Absent | Absent | Present | DNA Ligase-4 | AR | Very rare |
| Absent | Absent | Present | DNA PKcs | AR | Very rare |
| Low/Absent | Low/Absent | Low/Absent | Adenosine deaminase (ADA) | AR | 16% |
| Low/Absent | Low/Absent | Low/Absent | Purine nucleotide phosphorylase (PNP) | AR | Rare |
| Present | Present | Present | ORAI1 | AR | Very rare |
| Present | Present | Present | STIM1 | AR | Very rare |

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# Clinical Findings in SCID

- Skin / Mucosa
  - severe eczema
  - GVHD-like erythroderma
  - Persistent candidal rashes and thrush
- GI:
  - Chronic diarrhea (infectious or inflammatory)
  - Hepatitis
- Omenn’s syndrome

**Exam is usually completely unremarkable until they become infected.**

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# Severe Combined Immunodeficiency

- Lab findings:
  - Many (but not all) are lymphocytopenic
    - Lower limit ALC is **3800** in neonatal period

| Lymphocyte subpopulations | Neonatal (n = 20) | 1 wk-2 mo (n = 13) | 2-5 mo (n = 46) | 5-9 mo (n = 105) | 9-15 mo (n = 70) |
|---|---|---|---|---|---|
| Lymphocytes | 4.8 (0.7-7.3) | 6.7 (3.5-13.1) | 5.9 (3.7-9.6) | 6.0 (3.8-9.9) | 5.5 (2.6-10.4) |

| 15-24 mo (n = 33) | 2-5 yr (n = 33) | 5-10 yr (n = 35) | 10-16 yr (n = 23) | Adults (n = 51) |
|---|---|---|---|---|
| 5.6 (2.7-11.9) | 3.3 (1.7-6.9) | 2.8 (1.1-5.9) | 2.2 (1.0-5.3) | 1.8 (1.0-2.8) |

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# Newborn screening for SCID

Detect SCID before infants become symptomatic with infections and failure to thrive

Perform intervention: infection prophylaxis, avoid live vaccines and infectious exposures

Give immune system restoring treatments if required

SCID and Leaky SCID are primary targets of TREC NBS

Other conditions with insufficient naïve T cells are secondary targets

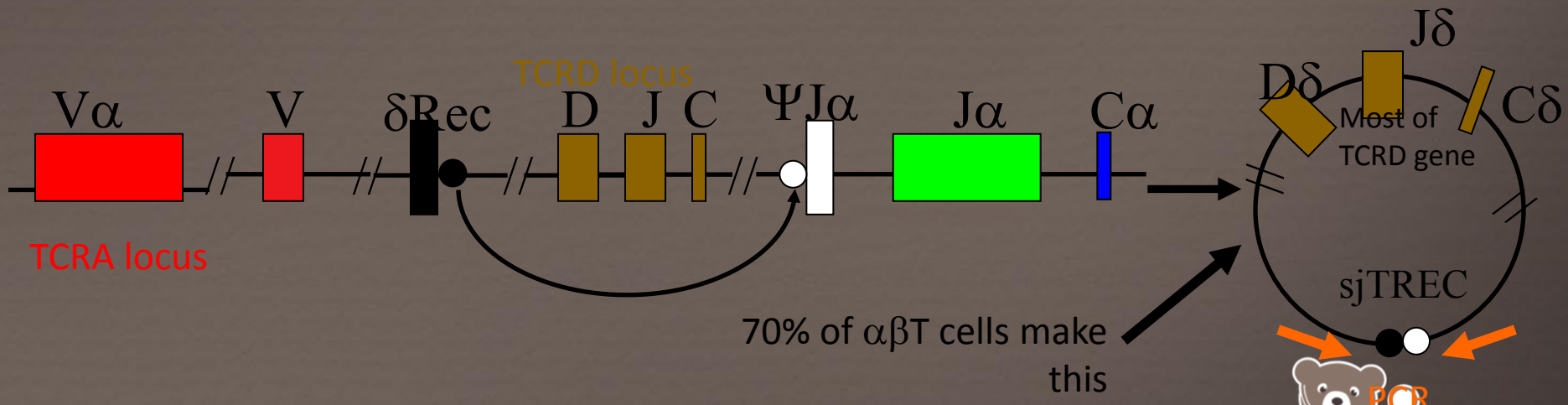
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# TREC Assay

## Thymus produces T cells with a diverse repertoire

- Antigen specificity arises by DNA recombination of T cell receptor genes.
- Excised DNA segments form circles (TRECs) as a byproduct.
- TRECs are stable and are detected by PCR.
- Newborns have the most TRECs; TRECs are diluted out as T cells undergo many divisions in the periphery.

## Generation of T Cell Receptor Excision Circles, TRECs




*Slide courtesy of Dr. Jennifer Puck, UCSF*

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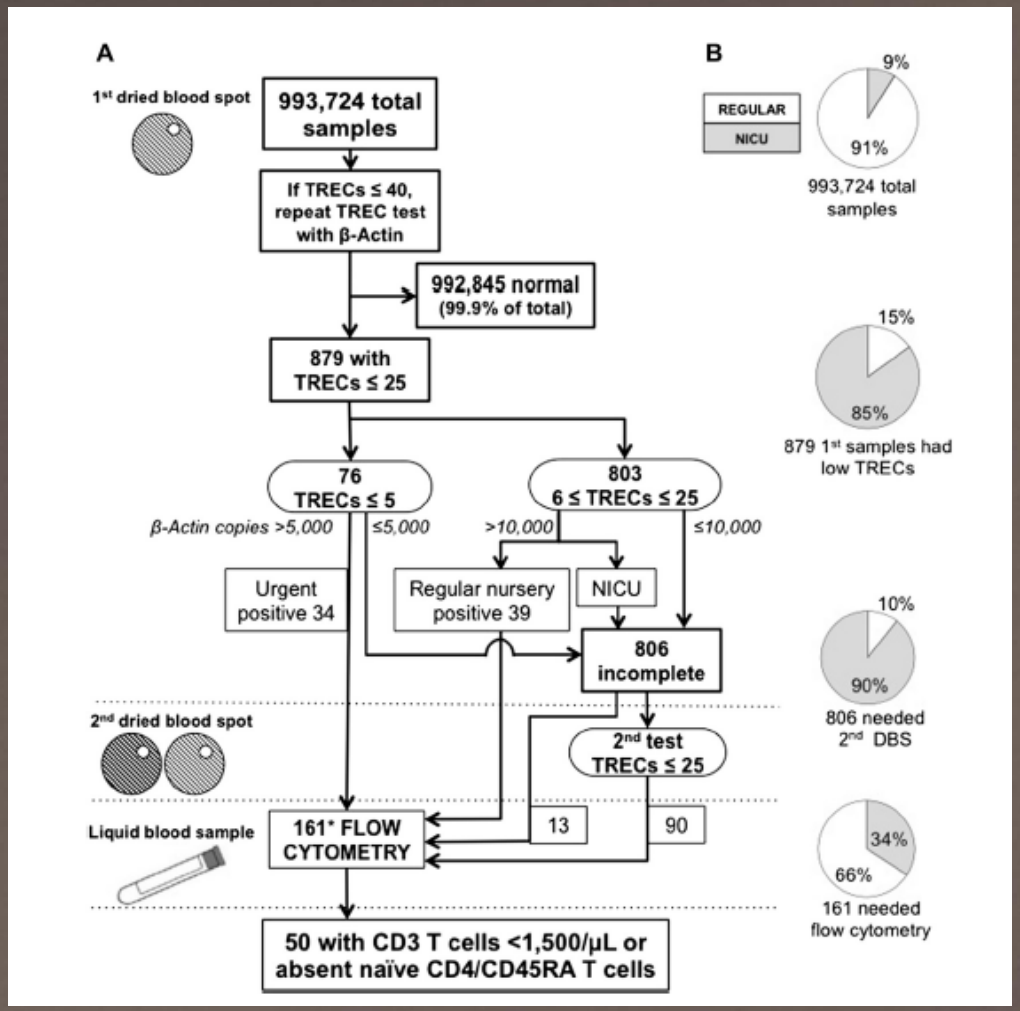
# TREC Assay

**Also catches other causes of congenital lymphopenia:**

- Ataxia Telangiectasia
- Complete Digeorge syndrome
- Down syndrome
- Congenital lymphangiectasia or chylothorax

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# CA SCID Screening: First 2 years



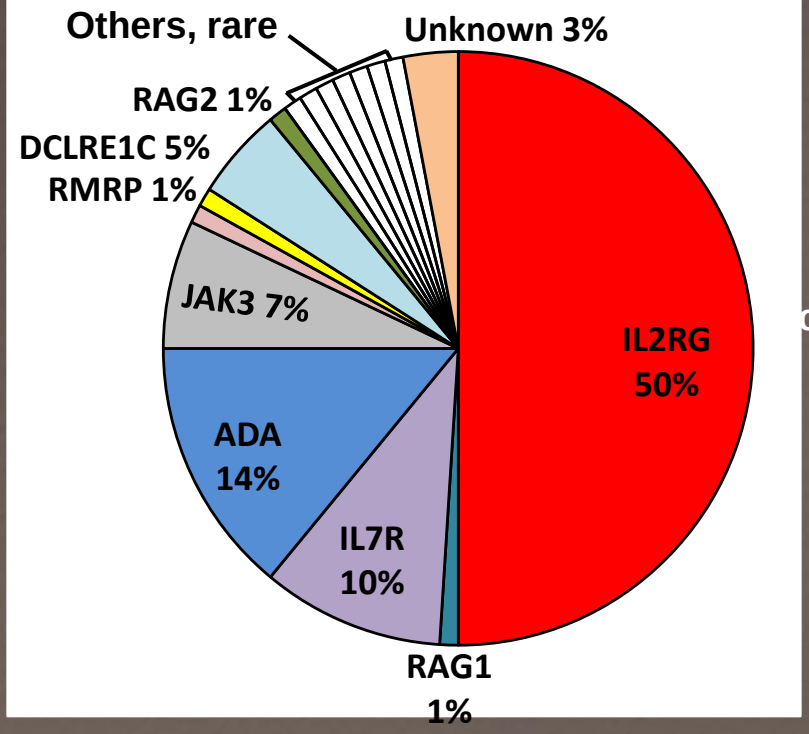

Kwan et al, JACI 2013

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# Genotypes of Typical and Leaky SCID

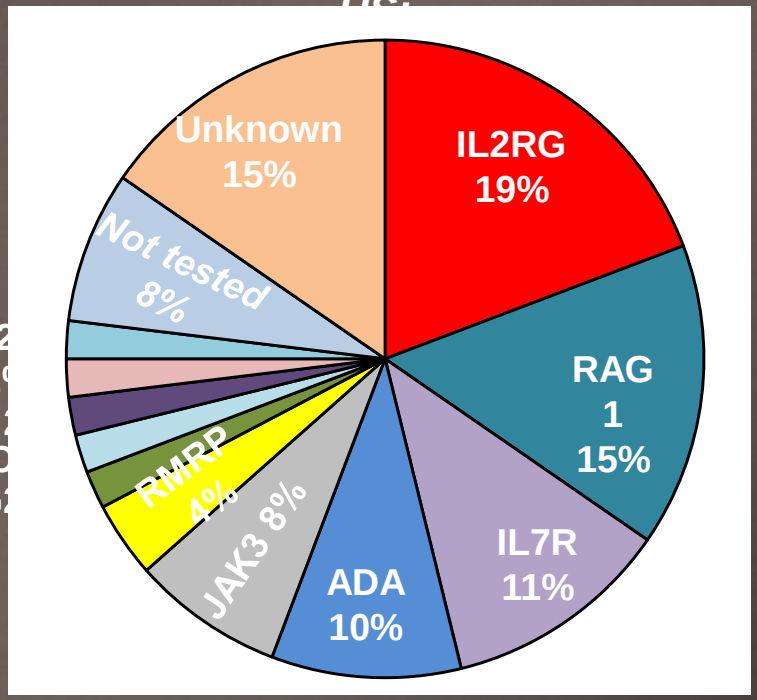
## Transplant center experience

*Estimated from reports by transplant centers*




## PROSPECTIVE SCREENING

*From 11 screening programs in US*




**From 52 infants nationally**

*Manuscript submitted, 2014*

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# Ways that PID may be missed by TREC NBS

Infant not screened, lapses in follow-up

Defect occurs after TCR recombination in thymus; T cells not reduced in number or diversity

- CD40L deficiency, Hyper-IgM syndrome, MHC II deficiency, ZAP70 deficiency

SCID gene defect sufficiently leaky to allow TRECs to be normal

Syndrome with variable T cell deficiency, for affected individuals with enough T cell generation to have TRECs above cutoff

Maternal neutralization of a metabolic defect (ADA), making TRECs normal at birth, reduced later

PID not involving T cells or not evident at birth

- XLA, CVID

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# What to do for Positive TREC Screens

**No live vaccines**

- Avoid Rotavirus vaccine

Isolation

- no sick contacts,
- minimize public outings with infant.

If child is breastfed: hold and check maternal CMV

- If mom is CMV IgG positive, breastfeeding should be halted, as many cases of breastfeeding CMV transmission have occurred.

Immunology consultation ASAP

# Call us anytime!

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## Back to the case…

- Rotavirus identified as **vaccine strain**
- **Treatment Course:**
  - Oral Immunoglobulin used for rotavirus
  - Successful Bone Marrow Transplant from a Matched-Unrelated Donor
  - Now thriving and off all medications

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# Thank you and Good Hunting!

**Immunology Section**

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