SCID/DiGeorge Syndrome: TRECs Update

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Objectives

- Describe severe combined immune deficiency (SCID)
- Describe the variety of abnormalities that can lead to a T cell deficiency
- Explain the diagnostic tests that might be used to further evaluate a patient for T cell immune deficiencies
- Describe the clinical presentation of DiGeorge Syndrome
- Describe T Cell Receptor Excision Circle (TREC) testing in newborns
- Identify other diseases that may be diagnosed with TRECs newborn screening
- Describe the standard management for a newborn with a positive newborn screen

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Primary Immune Deficiency

- Immune deficiency not caused by other factors (secondary immune deficiency)
  - Disease
  - Medications
  - Malnutrition
- Estimated 200 primary immune deficiency diseases
- 1:1,200 live births have an immune deficiency

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Primary Immune Deficiency

- Humoral (antibody, B lymphocytes affected)
  - Selective IgA deficiency or common variable immune deficiency
- Cellular (T lymphocytes affected)
  - DiGeorge Syndrome
- Combined (T, and/or B, and/or NK cells affected)
  - SCID subtypes
- Phagocytic
  - Chronic granulomatous disease
- Primary ciliary dyskinesia

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Case 1

- HPI:
  - Female born via C section at 38 weeks and 5 days due to failure of progression of labor.
  - Infant was born without adequate respiratory effort. However, by 4-5 minutes, baby improved.
  - Patient transferred to the neonatal ICU for further observation.

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Case 1

- Family History
  - Mother: healthy
  - Father: healthy
  - Paternal aunt has severe combined immune deficiency
  - Maternal 1st cousin and paternal uncle died in infancy
  - 2 paternal 1st cousins with primary ciliary dyskinesia
- Social history
  - Significant for being Irish travelers
  - High incidence of consanguinity

Case 1

- Physical Exam
  - Vitals: RR 29, SpO2 100%, HR 108, BP 56/35, Temp 36.7°C
  - General: no acute distress
  - HEENT: normocephalic, fontanelles were normal in size, normal eyes without conjunctival erythema or drainage, well positioned ears and normal pinnae, patent nares with normal mucosa, oropharynx is clear, palate was intact
  - Respiratory: clear to auscultation, unlabored breathing
  - Cardiovascular: regular rate and rhythm, normal S1, S2, no murmurs or gallops

Case 1

- Physical Exam:
  - GI: normal appearance, soft, non-tender, without organ enlargement or masses
  - GU: normal female external genitalia
  - Neurologic: moves all extremities, good tone
  - Spine: spine intact
  - Extremities: normal
  - Skin: pink without rash

Case 1

Lab	Level	Interpretation
Hemoglobin	16.3	Low
Hematocrit	48.6	Low
Platelet Count	313	Normal
White Blood Cells	14.4	High
Segmented Neutrophils (%/Abs)	63%/11.3	Normal
Bands	15%	High
Lymphocytes (%/Abs)	9%/1296	Low
Monocytes	12%	Normal
Eosinophils (%/Abs)	1%/1.4	Normal

Case 1

- IgG 941 (614-1536 mg/dL)
- IgA <10 (0-7 mg/dL)
- IgM <20 (6-23 mg/dL)

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Case 1

Lymphocyte Subsets	Results
CD3+ T cells %	0.4% (58-67%)
CD3 absolute	<4 (1700-3600)
CD4+ T cells %	0.2% (38-50%)
CD4 absolute	1 (1700-2800)
CD8+ T cells %	0.3% (18-25%)
CD8 absolute	2 (800-1200)
CD16/56 NK cells %	95.9 (8-17%)
CD16/56 absolute	435 (300-700
CD19 B cells %	0 (19-31%)
CD19	0 (500-1500)

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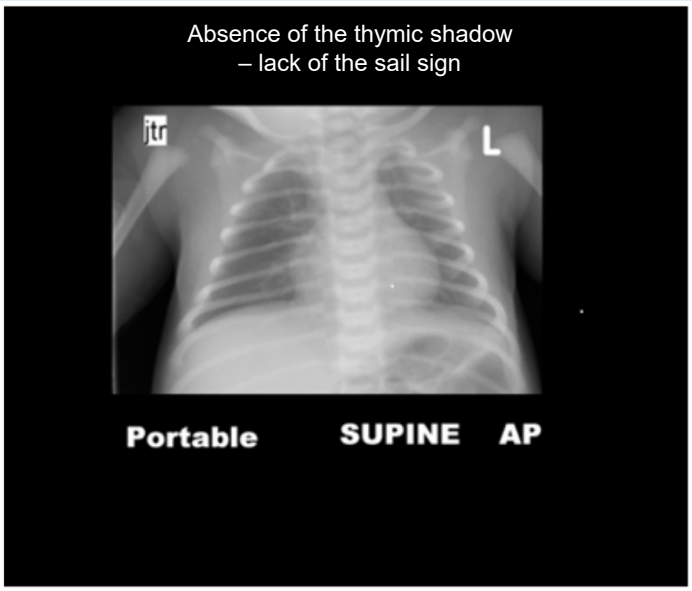
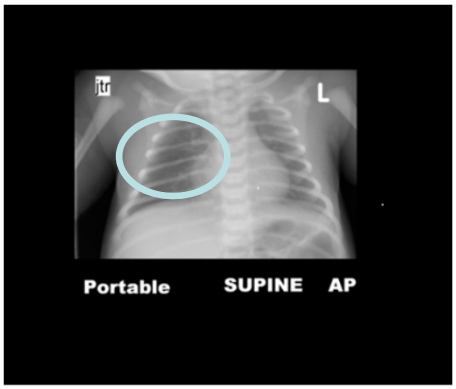
Absence of the thymic shadow
– lack of the sail sign

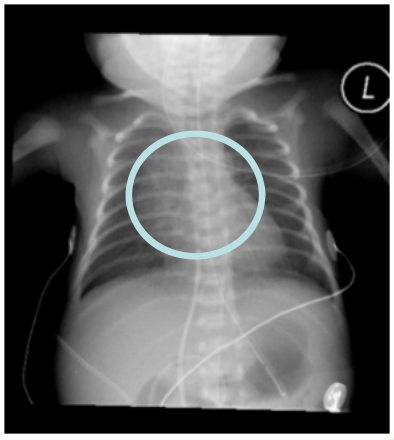


Case 1



Thymus shadow is missing

Normal CXR



Normal cardiothymic silhouette

Case 1

- So what is the diagnosis?
- SCID:
  - –T-B-NK+
- Genetic evaluation:
  - –RAG-1 Defect

Severe Combined Immune Deficiency (SCID)

- Initially described in 1950
- Syndrome caused by mutations in different genes whose products are necessary for T/B/NK cell development
- Leads to early death from overwhelming infection within the first year of life if not transplanted
- 1:40,000-1:50,000 live births
  - 1:2,500 in Navaho population
- 45% are X-linked SCID

Clinical features

- Within the first few months of life:
  - Recurrent episodes of diarrhea, pneumonia, otitis, sepsis and cutaneous infections
  - Failure to thrive (may be normal initially)
- Opportunistic organisms:
  - Candida albicans, Pneumocystis jirovecii, varicella, adenovirus, parainfluenza, herpes viruses, cytomegalovirus, rotavirus, measles, norovirus and Epstein-Barr

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Clinical features

- Attenuated vaccine organisms can cause severe or fatal infection
  - Polio, rotavirus, varicella and BCG
- Diagnosis may be delayed several months since infants look normal and maternally-derived antibodies provide some protection in early infancy
  - IgG crosses the placenta
    - Nadir 4-6 months or earlier
  - IgA and IgM may be low and still at age appropriate levels

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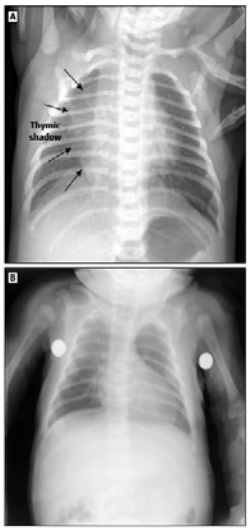
Clinical features

- Small thymus (less than 1 gm)
  - Fails to descend from neck
  - Few thymocytes
  - Lacks corticomedullary distinction & Hassall's corpuscles
  - Presence of a thymic shadow does not rule out SCID as it may be present in rare forms



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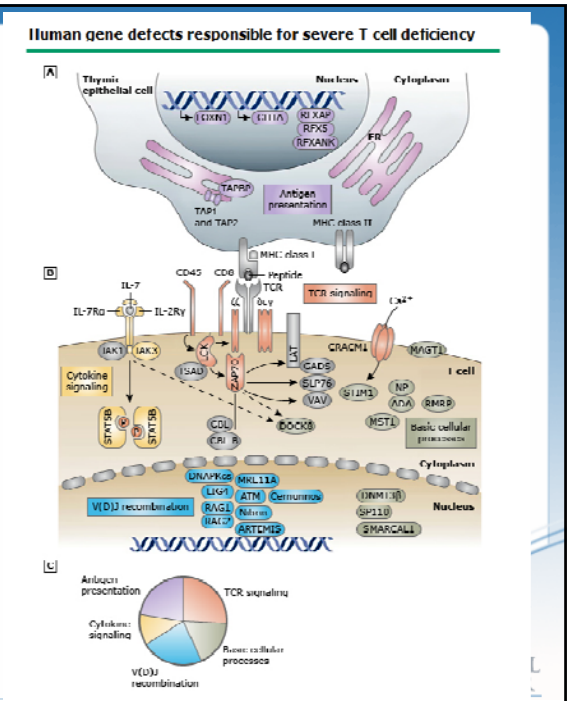
A defect may occur at nearly any area in the T cell receptor activation, cell signaling, or with subsequent gene transcription to cause a T cell deficiency



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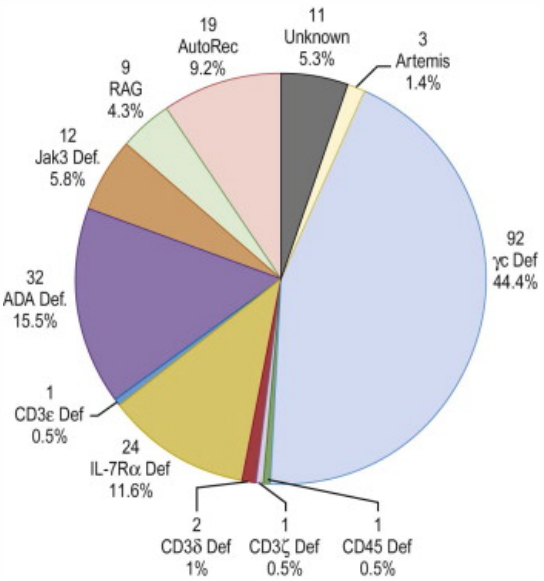

Severe combined immunodeficiency (SCID) classification and gene defects*

T-B+NK- SCID	
X-linked SCID, common gamma chain (gamma-c)*	*IL2RG*
Janus kinase 3	*JAK3*
T-B+NK+ SCID	
Interleukin-7 receptor alpha chain (CD127)	*IL7RA*
Actin-regulating protein coronin 1A (CORO1A)	*CORO1A*
CD3 chain components	
CD3 delta	*CD3D*
CD3 epsilon	*CD3E*
CD3 zeta	*CD3Z*
CD45	*PTPRC*
T-B-NK+ SCID	
Recombinase activating genes 1 and 2	*RAG1, RAG2*
Artemis	*DCLRE1C*
DNA protein kinase catalytic subunit (DNA-PKcs)	*PRKDC*
DNA ligase IV	*LIG4*
Cernunnos/XRCC4-like factor (XLF)	*NHEJ1*
T-B-NK- SCID	
Adenosine deaminase	*ADA*
Reticular dysgenesis	*AK2*

The defects listed in *italics* are the most common forms of SCID.

NK: natural killer; *IL2RG*: interleukin-2 receptor common gamma chain; CD: cluster of differentiation; CORO1A: coronin-1A; PTPRC: protein tyrosine phosphatase, receptor type, C; *DCLRE1C*: DNA-crosslink repair protein 1C; PRKDC: protein kinase, DNA-activated, catalytic subunit; XRCC4: X-ray repair complementing defective in Chinese hampster 4; NHEJ1: nonhomologous end-joining factor 1; AK2: adenylate kinase 2.
* Some defects in these genes lead to milder, non-SCID combined immunodeficiencies.
• Some patients with X-linked SCID have NK cells present at low levels and would thereby be classified as having T-B+NK+ SCID.

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SCID Evaluation

- Peripheral lymphocyte count (infant or cord blood)
- TRECs (T cell excision circles) analysis
  - Neonatal screening
  - Measures T cells emigrating from the thymus (mature)
  - Low to absent in neonates who make no or few T cells
  - Slightly lower in premature infants
- Lymphocyte subsets (T, B, NK cell enumeration)
- Lymphocyte proliferation (mitogens and antigens)
- Immunoglobulin levels (IgG, IgA, IgM, IgE)
- Specific antibody responses
  - If > 6 months of age

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SCID Evaluation

- Strong suspicion for SCID suspicion. (or another T cell immune deficiency):
  - Absolute lymphocyte count < 2500 cells/mm3
  - T cells making up less than 20% of the total lymphocytes
  - Lymphocyte stimulation to mitogens is < 10% of the normal control
  - Absence of the thymus on CXR

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SCID Evaluation

- Serum immunoglobulin concentrations may be low or absent
  - Even if B cells are present, they do not make immunoglobulins
    - Possibly even after transplantation
  - May have normal IgG levels for the first few months of life
    - Transplacental maternal transfer
- Lack of antibody formation after immunization
- T cells always diminished or absent
- Variable presence/absence of B/NK cells determines the defect

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X-linked SCID (T-B+NK-)

- About 45% of infants with SCID
- Defect on X chromosome encoding the cytokine receptor subunit common gamma chain, IL2 R gamma
  - Diagnosed on flow cytometry
  - Receptor subunit shared by six different cytokine receptor complexes: IL-2, 4, 7, 9, 15 and 21
  - Gamma-chain is also involved in growth hormone receptor signaling
    - Growth failure may be partially due to this

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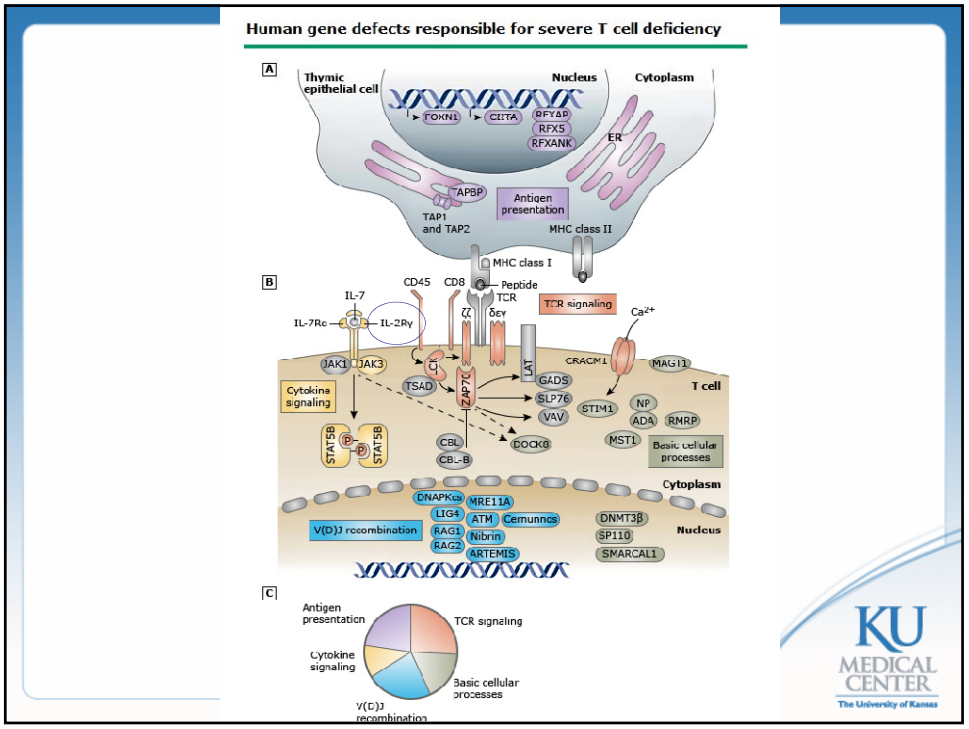
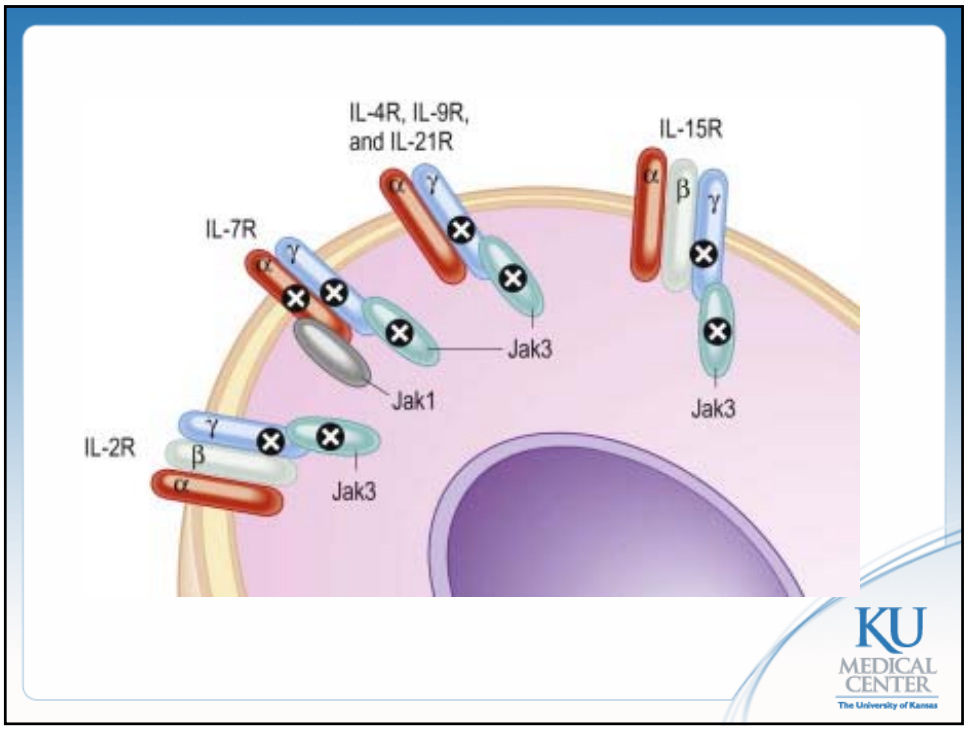

Human gene defects responsible for severe T cell deficiency
A
Thymic epithelial cell
Nucleus
Cytoplasm
FOXN1
CIITA
RFXAP
RFX5
RFXANK
ER
TAPBP
TAP1 and TAP2
Antigen presentation
MHC class II
MHC class I
B
IL-7
IL-7Rα
IL-2Rγ
CD45
CD8
Peptide
TCR
ζζ
δεγ
TCR signaling
Ca2+
JAK1
JAK3
Cγ
ZAP70
LAT
GRAM1
MAGI1
TSAD
GADS
SLP76
VAV
STIM1
NP
ADA
RMRP
T cell
Cytokine signaling
STAT5B
P
CBL
CB-L-B
DOCK8
MST1
Basic cellular processes
Cytoplasm
DNAPKcs
MRE11A
LIG4
ATM
Cernunnos
RAG1
Nibrin
RAG2
ARTEMIS
V(D)J recombination
DNMT3β
SP110
SMARCAL1
Nucleus
C
Antigen presentation
TCR signaling
Cytokine signaling
Basic cellular processes
V(D)J recombination


IL-4R, IL-9R, and IL-21R
IL-15R
IL-7R
Jak3
Jak1
Jak3
IL-2R
Jak3

Autosomal Recessive SCID

- First described in 1950 in Switzerland
- More common in Europe
- 12 genetic types
  - ADA, JAK3, IL-7 receptor alpha, RAG-1 or RAG-2, Artemis, ligase 4 deficiency, DNA-dependent PKCs (catalytic subunit), CD3 (delta, epsilon or zeta) and CD45 deficiencies
- May present as Omenn Syndrome
  - "Leaky" hypomorphic SCID

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ADA deficiency (T-B-NK-)

- 16% of SCID patients
- Accumulation of adenosine, 2'-deoxyadenosine and 2'-O-methyladenosine
  - Latter two metabolites lead directly or indirectly to apoptosis of thymocytes and circulating lymphocytes
- More profound lymphopenia than other SCID types
  - Absolute lymphocyte count < 500/uL
- Treatment: transplant, PEG-ADA

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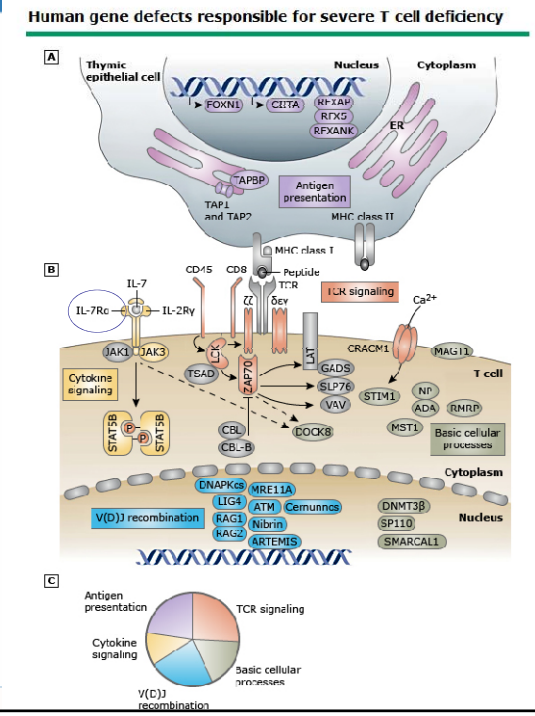
IL-7 receptor alpha chain deficiency (T-B+NK+)

- Third most common SCID phenotype
- IL-7 receptor alpha is specific only for T-cell development
- Can present as Omenn syndrome
- Patients acquire normal B cell function after haploidentical bone marrow stem cell transplantation without donor B cells

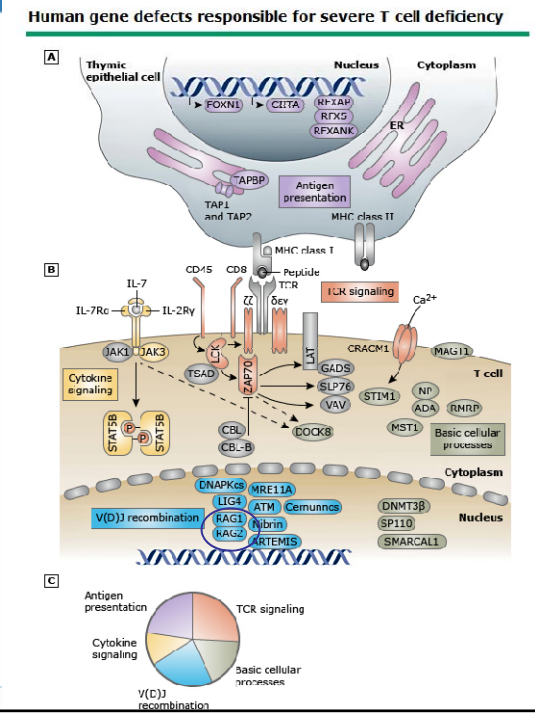


RAG-1 and RAG-2 (T-B-NK+)

- Involved with VDR rearrangement of T and B cell antigen receptors
- Can also present with Omenn syndrome
- Fatal unless corrected with transplantation

This is our patient's diagnosis

Transplantation winter 2015, doing well!



Radiosensitive

- Inability to repair DNA damage with several types;
  - Artemis (T-B-NK+)
  - Ligase IV Deficiency (T-B-NK+)
  - DNA-dependent protein Kinase catalytic subunit deficiency (T-B-NK+)
  - Nijmegen breakage syndrome
  - Cernunnos/XLF deficiency
- Avoid all unnecessary imaging

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Omenn Syndrome

- Leaky SCID -Autosomal recessive
  - Hypomorphic missense mutations:
    - RAG1 and RAG2, IL-7 Receptor α gene, Artemis, DNA-Ligase IV, common gamma chain, ZAP-70, DNA dependent PKC deficiency.
  - Abnormal auto-reactive T cells
    - Low T cells and no B cells
    - Symptoms similar to GVHD: rash (erythroderma), eosinophilia, FTT, lymphadenopathy, diarrhea, hepatosplenomegaly, elevated IgE, low IgG/IgM/IgA

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Differential Diagnosis

- Extreme malnutrition
- HIV/AIDS
- Cystic fibrosis
- Wiskott-Aldrich (x-linked)
  - WASp gene mutation
- DiGeorge syndrome
- Hyper IgM syndrome

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Doctor's Strike

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Case 2

- HPI: 3 day old infant having problems with hypoxia and turning blue, found to have a heart defect on exam and has been placed in the NICU. ECHO is done and it seems the baby has a heart defect. Labs show a low calcium level and has intermittent facial tetany. He is not feeding well.

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Case 2

- Physical Exam
  - Vitals: RR 55, SpO2 85%, HR 180, BP 68/35, Temp 36.7°C
  - General: mild acute distress that is worse when crying
  - HEENT: normocephalic, fontanelles were normal in size, normal eyes without conjunctival erythema or drainage, low set ears, patent nares with normal mucosa, short philtrum, oropharynx is clear, cleft palate
  - Respiratory: clear, tachypnea
  - Cardiovascular: tachycardia, +murmurs

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Case 2

- Physical Exam:
  - GI: normal appearance, soft, non-tender, without organ enlargement or masses
  - GU: normal male external genitalia
  - Neurologic: moves all extremities with normal tone, has some intermittent spasms noted
  - Spine: spine intact
  - Extremities: normal
  - Skin: pink without rash

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Case 2

- FH:
  - Mother and father are healthy
  - No siblings
  - No other early childhood deaths in the extended family, no immune abnormalities
- SH:
  - No consanguinity
  - Family is of unknown descent

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Case 2

Lymphocyte Subsets	Results
CD3%	0.4% (58-67%)
CD3 absolute	<4 (1700-3600)
CD4%	0.2% (38-50%)
CD4 absolute	1 (1700-2800)
CD8%	0.3% (18-25%)
CD8 absolute	2 (800-1200)
CD16/56%	48.5 (8-17%)
CD16/56 absolute	699 (300-700)
CD19%	50.6 (19-31%)
CD19	729 (500-1500)

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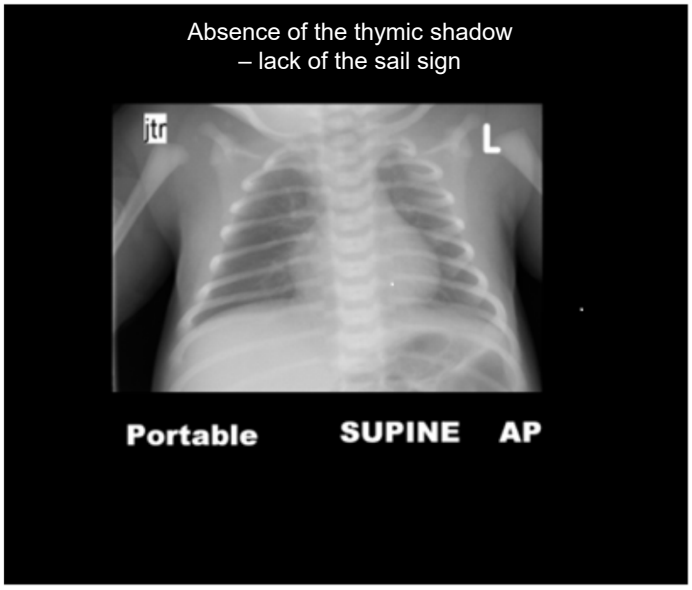
Absence of the thymic shadow
– lack of the sail sign



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Case 2

- So what is the diagnosis?
  - –T-/B+/NK+ SCID?
- DiGeorge Syndrome
  - –22q11.2 deletion
  - –Defect in the development of the pharyngeal pouch system

DiGeorge Syndrome

- Clinical presentation (CATCH 22)
  - – C – Cardiac anomalies
  - – A – Abnormal facies
  - – T – Thymus aplasia
    - Hypoplasia in partial DiGeorge
  - – C – Cleft palate
  - – H – Hypocalcemia/Hypoparathyroidism
  - – 22 – 22q11.2 deletion

Clinical Non-Immune Findings

- Palate abnormalities
- Cardiac abnormalities
- Developmental delay
  - Speech delay
  - Learning disabilities
- Ophthalmologic abnormalities
- Hypocalcemia
- Psychiatric disorders
- Skeletal abnormalities
- Renal, neurologic, dental abnormalities
- Short stature

http://byebyedoctor.com/wp-content/uploads/2011/06/digeorge-syndrome-2.jpg

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DiGeorge Syndrome

- Complete DGS is a form of SCID
  - Found in <1% of patients with 22q deletion syndromes
  - Thymus is absent
  - T lymphocytes are absent
  - Fatal unless treated promptly with thymic or bone marrow transplant
- Diagnosis
  - Newborn screening
  - Lymphocyte subsets (T, B, NK cells)

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Phenotypic Findings

- Ocular hypertelorism
- Upslanting palpebral fissures
- Low set posteriorly rotated ears
- Widened area below nasal bridge
- Hooded eyelids
- Bulbous nose tip
- Micrognathia
- Short philtrum
- High arched palate
- Cleft palate / bifid uvula
- Tapered fingers

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Diagnostic criteria for DiGeorge syndrome

Definitive diagnosis*
Male or female patient with reduced numbers of CD3+ T cells (less than 500/mm^3) and two of the three following characteristics:
1. Conotruncal cardiac defect (truncus arteriosus, tetrology of Fallot, interrupted aortic arch, or aberrant right subclavian).
2. Hypocalcemia of greater than three weeks' duration that requires therapy.
3. Deletion of chromosome 22q11.2.
Probable diagnosis*
Male or female patient with reduced numbers of CD3+ T cells (less than 1500/mm^3) and a deletion of chromosome 22q11.2.
Possible diagnosis*
Male or female patient with reduced numbers of CD3+ T cells (less than 1500/mm^3) and at least one of the following:
1. Cardiac defect.
2. Hypocalcemia of greater than three weeks' duration that requires therapy.
3. Dysmorphic facies or palatal abnormalities.

* Patients with a definitive or probable diagnosis are assumed to have a greater than 98 and 85 percent probability, respectively, that in 20 years they will still have the same diagnosis. Patients with a possible diagnosis are those that have some but not all of the characteristic clinical or laboratory findings of a particular disorder.

From Conley ME, Notarangelo LD, Etzioni A. Clin Immunol 1999; 93:190.

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Summary T Cell Deficiencies

SCID

- Defect in T cell production
- +/- NK and/or B cell #s
- Opportunistic organisms
- Imaging: small or absent sail sign (small thymus)
- Absent immunoglobulins
- Diagnosis: TRECs analysis, total lymphocyte count, genetics
- Treatment:
  - HSCT, IVIg, antimicrobials

DiGeorge Syndrome

- Defect in T cell production
- Normal NK and B cell #s
- Opportunistic organisms
- Imaging: absent sail sign in complete
- Absent/low immunoglobulins
- Diagnosis: TRECs analysis, genetics
- Treatment: thymus or HSCT, IVIg

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T Cell Receptor Excision Circles (TRECs)

- TRECs analysis newborn screening
  - Detect T cell defects with screening
  - Sensitive, specific
  - Low false positive rate
  - Cost effective

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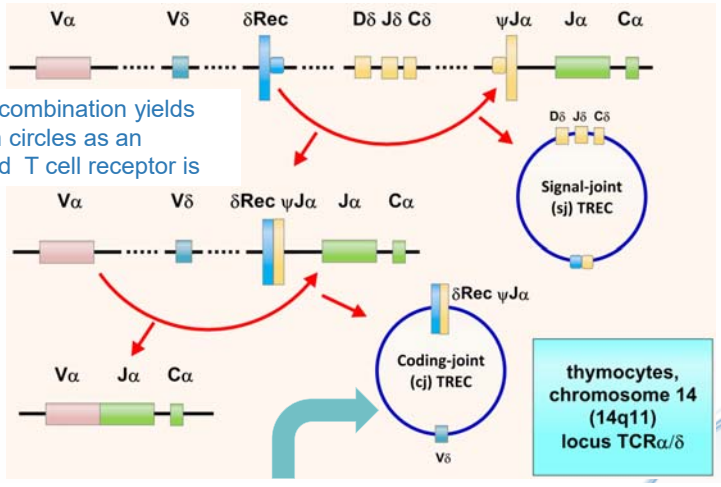
TRECs Analysis



VDJ Recombination yields excision circles as an activated T cell receptor is formed

These excision circles are discarded in the form of TRECs

TRECs analysis

- Severe Combined Immune Deficiency
- Omenn's Syndrome (Leaky SCID)
- DiGeorge Syndrome
- Ataxia Telangiectasia
- Trisomy 21
- Pre-term infants
- T cell lymphopenia secondary to other systemic disorders
  - Cardiac abnormalities
  - Gastrointestinal abnormalities

TRECs Cost Savings

- Cost vs benefit ratio – $4.36
  - $4 saved for every $1 spent
- Treatment costs
  - $350,000 per baby savings in early vs late treatment
- Life value – $7.9 million
- $2.8 million saved per year if 1 baby is saved every 3 years
- Pilot in Kansas 2017 – Go-live 2018

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Treatment

- **Pediatric emergency**
- Hospitalization in most cases for isolation
- Antimicrobial prophylaxis
- Intravenous immunoglobulin
- HLA-identical or haploidentical donor bone marrow transplantation needed for survival
  - Prior to 3.5 months of life: 95% chance of survival at 20 years
  - After 3.5 months of life: <70% chance of survival

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Positive TRECs Screening

- Contact the family
  - Inform them of the results, provide information
  - Start additional testing
  - Alert mom to stop breast feeding until CMV status can be assessed
  - Avoid any exposure to live viral vaccines
- Any evidence of infection
  - Refer to Children's Mercy Hospital or the University of Kansas Medical Center emergently
- Blood products needed
  - Ensure they are leuko-reduced, irradiated, and CMV negative

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SCID

- Positive screen = further testing
  - Repeat if premature/low birth weight
  - Complete blood count
  - Lymphocyte subsets (T, B, and NK cell panel)
  - Quest stat labs (kits will be present at draw stations)
  - Report confirmatory findings to the newborn screening program at 785-291-3363
- Immunology consultation
  - Lymphocyte proliferation
  - Immunoglobulins
  - Facilitate transfer/admission
- Bone Marrow Transplantation

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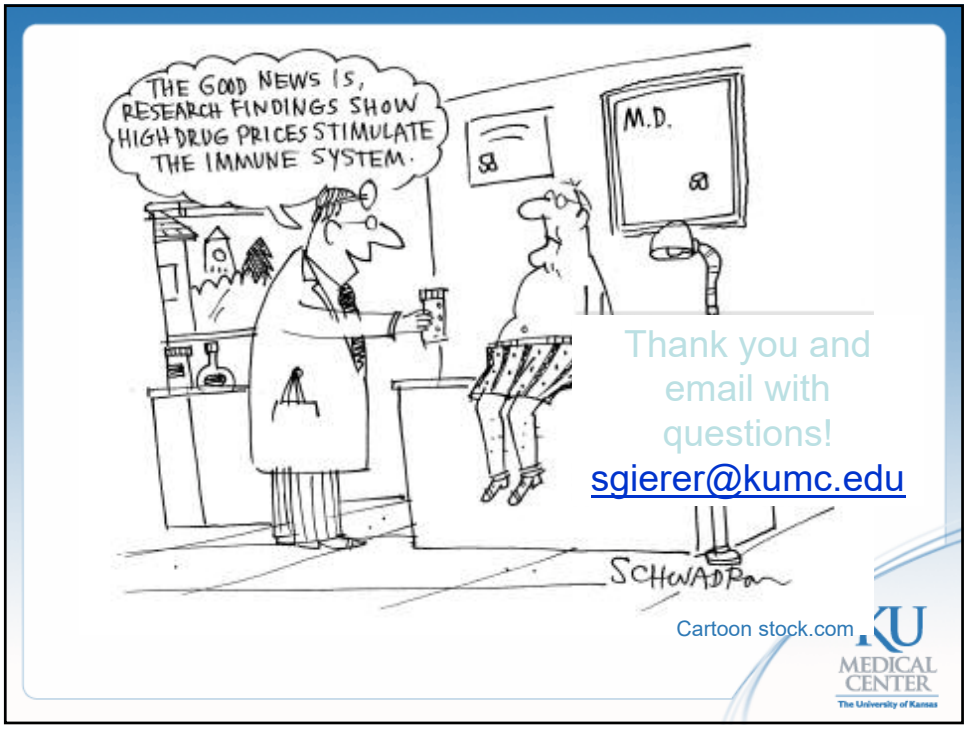
Immunology

- Dr. Selina Gierer
  - KU Medical Center
  - Kansas City, KS
  - 913-588-5000
    - Page the Immunology faculty/fellow on call
- Dr. Nikita Raje
  - Children's Mercy
  - Kansas City, MO
  - 816-234-3390
    - Page the Immunology faculty/fellow on call

Additional Information

- Genetics Home Reference
  http://ghr.nlm.nih.gov/condition/x-linked-severe-combined-immunodeficiency
- SCID.net
  http://www.scid.net/
- Immune Deficiency Foundation
  http://primaryimmune.org/



Thank you and email with questions!

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