

# **Newborn Screening for SCID in a High Risk population**

Why Arizona should include TREC  
screening in the routine newborn  
screen

# Silly Wabbit, TRECs are for SCIDS!

(Apologies to General Mills and the fans of TRIX cereal...)



# Premise

- TREC screening for SCID and other T cell deficiencies is a low cost, highly specific and sensitive test that is easily incorporated into a NB screening protocol
- Arizona is home to 6 NA tribes with disproportionately high rates of SCID that would benefit greatly from universal screening protocols.
- Early detection and treatment of SCID and other T cell deficiencies can have great impact on the lives of affected children

# A case history

- 2mo old F infant presents with resp distress and shock
- Baby born as term healthy Navajo female infant to a 19yo G1 mom from Page, AZ.
- Home with mom at 48 hours of age

# A case history

- Resuscitation in Page ED with intubation, mechanical ventilation, vasopressors, blood transfusion.
- Pulm hemorrhage as well as pneumonitis on CXR
  - No thymus on CXR
- Transferred to Cardon Children's Hospital. S Pneumoniae sepsis.

# A case history

- Improvement in sepsis with antibiotics and supportive care
- However, baby with encephalopathic neuro exam. CMV PCR(+) in CSF
  - From breast feeding?
  - From transfusions?
- Transferred to UCSF at 3 weeks into hospitalization for stem cell transplantation

# A case history

- Peripheral stem cell transplant, haplotype matched donor
- Now 3 yo, T cell engrafted
  - Routine IVIG monthly
- Severe neurologic damage

# A happier case

- Term healthy Navajo baby born to a 23 yo G3 mom at Tuba City
- Presents at 6 week of age with croup and fever
  - Feb 2009- RSV season...
    - but RSV and Flu rapid tests(-)
  - Has a prolonged course- still has stridor at 48 hrs
  - Ulceration noted perianal area
  - No thymus on CXR

# A happier case

- WBC- 8.1K, ALC 1500
- Transferred to PCH for evaluation, R/o SCID
- SCID-A diagnosis made
- Stem cell transplant within 2 weeks
  - HLA matched sibling donor
- Full engraftment at 6mos
  - Normal development

# WHO Criteria Screening

- Condition an important health problem
- Cost of case finding reasonable
- Recognizable in latent phase
- Effective treatment available
- Acceptable to population tested

# SCID meets these criteria

- **A lethal disorder** not detectable at birth by routine examination
  - Death comes from overwhelming infection in infancy
- **Incidence of disease is significant** in the US but especially in AZ
- **TREC testing now available** to screen patients
  - Cost per test as low as \$6 per test commercially
- **Confirmatory testing available**
  - Flow cytometry
- **Treatment available- potentially curative**
  - Stem cell transplant
  - Gene therapy

# SCID

- Lack of cellular immunity T-, B- SCID
  - Missing T lymphocytes – responsible for defense against viral and fungal infection, facilitate antibody production and recognition of foreign proteins and germs, immune memory cells
  - Missing B lymphocytes- make antibodies (immunoglobulins) responsible for processing germs for destruction by other elements of the immune system, give immune memory against many infections
  - Bacterial, viral, fungal infections can all become lethal, even with antimicrobial treatment

# Natural history of SCID

- Usually are born looking normal
- Mouth Ulcers/perianal ulcers
- Recurrent thrush
  - Fungal infection of the mouth
- Failure to gain weight
  - Recurrent diarrhea
- Skin rash
- Inability to fight off infection acquired in 1<sup>st</sup> year of life
- Usually fatal in by age 2 if not treated

# SCID--Diagnosis before NB screening

- how to make early diagnosis possible?
- Screening tests- CXR, CBC with ALC
- If concerned
  - lymphocyte subsets and function tests
    - Requires live cells
    - Requires 8 ml blood
    - Requires Fed Ex to reference lab
    - potential delay of 1-2 weeks to get results back
    - cost ~\$800

# SCID dx

- Problem: when to be concerned?
- If no family history, **SOMETHING BAD HAS TO HAPPEN TO TRIGGER THE DX EVALUATION.**
  - That something bad could be a fatal event or one that leaves long lasting consequences
  - **avg. age at diagnosis usually 4-6 mos.**

# Treatment of SCID

- Give them a new immune system
  - Bone marrow transplant
  - Peripheral stem cell transplant
  - Umbilical cord blood transplant
- All are a source of the stem cells that eventually will mature into lymphocytes
- Donor- usually a sibling or parent
  - BMT services available in AZ and CA

# Why is this specifically important for AZ?

- Athabascan tribes have a specific gene mutation on the Artemis gene ( 10p) that is associated with SCID
- Carrier frequency estimated at 1:30 on the Western Navajo reservation
- Incidence of SCID 1:2000 births Western Navajo
  - *As frequent as many of the other conditions we screen for- and is potentially CURABLE with early intervention*

# SCID-A

- Athabascan type SCID- T-B- NK+
- Higher incidence in Athabascans:  
Dene, Navajos, and Apaches than any  
other ethnic group
  - 1<sup>st</sup> described in 1982- descriptive paper on 4 children seen  
at Denver
- General population incidence 1:100,000
  - Western Navajo population incidence 1:2000

# SCID-A

- 46 Athabascan children in the Southwest since 1978
  - 31 Navajo children
  - 3 Athabascan (Dene) children from NW Canada
- Cases found in San Carlos, Whiteriver, Mescalero (NM), Jicarilla (NM) Apache tribal members and Ramah Navajo

# SCID-A outcome

- Success of therapy directly correlated with early identification of patients and transplant < 2mos of age
- Many children with SCID have had delay in diagnosis leading to permanent morbidity or death

# Pilot projects results -

Pilot	Annual Births/Pilot Target	Date: Start of Screening	Months Screening	Number of Infants Screened as of March 31, 2011	SCID	SCID Variant	Non SCID
Wisconsin	69,232	1/1/2008	39	225,004	4	0	7
Massachusetts	77,022	2/1/2009	26	161,707	1	0	14
Navajo Nation	2,000	2/1/2009	26	1,297	0	0	0
California	510,000	8/1/2010	8	340,000	5	5	5
Puerto Rico	45,620	8/1/2010	8	29,115	0	0	3
New York	236,656	9/30/2010	6	118,328	2	2	9
Louisiana	65,268	10/1/2010	6	32,634	0	0	1
Total			119	914,557	12	7	35

Courtesy: Amy Brower & SACHDNC

Data as of May 2011

# Navajo Nation pilot

- CDC Grant received to start screening
- 2 year project- screened ~2000 babies at Chinle and Tuba City
  - 60% participation
  - Test was acceptable to population
    - Most refusals were because of belief that baby was healthy and did not need testing
    - 3 false positives found, normal on recheck
- One infant with T cell deficiency and DiGeorge variant found by screening

# Navajo Nation screening

- Donation of 6000 tests from Perkin Elmer genetics
- Implemented universal screening Feb 2012 at 6 delivering hospitals on NN
  - 1 still pending.
- 550 children screened as of May 31, 2012
- *But what about those babies who are not born on the reservation?*

# Incidence calculations

Diagnosis	Incidence	State*			
		CA	NY	MA	WI
<i>SCID</i>		1 in 68,000	1 in 59,164	1 in 161,707	1 in 56,251**
<i>SCID Variant</i>		1 in 68,000	1 in 59,164	NA	NA
<i>SCID + SCID Variant</i>		1 in 34,000	1 in 29,582	1 in 161,707	1 in 56,251**

***Incidence is generally higher than previously reported***

# HHS recommendation

- Jan 2010- Advisory Committee for Heritable Disorders in Newborns and Children (ACHDNC) recommends to HHS to add for inclusion to mandatory NB screening panel
  - May 2010 Sibelius formal announcement
- 2011- 10 states/terr have adopted
  - Wisc, Mich, Mass, Calif, Conn, Colorado, Del, Louisiana, New York, Puerto Rico
  - Navajo Nation, Penn, Texas pilot programs
  - Vetoed Fla
  - Texas just approved May 2012 after previous veto ! (800,000 tests per year!)

# Arizona

- 2010 census
  - 4.6% AIAN population
  - 5.5% with more than one race listed
  - 21 federally recognized tribes
    - 6 Athabascan tribes

# AZ births

- ADHS stats 2010
  - Births- 6.8% of AZ births with AI/AN mother (5815 births)
  - Over 87,000 births per year
- Likely to find 2 to 3 cases SCID per year
  - Likely to find more cases of other t cell deficiencies annually

# Summary

- TREC screening for SCID and other T cell deficiencies is a low cost, highly specific and sensitive test that is easily incorporated into a NB screening protocol
- Arizona is home to 6 NA tribes with disproportionately high rates of SCID that would benefit greatly from universal screening protocols.
- **Early detection and treatment of SCID and other T cell deficiencies can SAVE LIVES and \$\$**

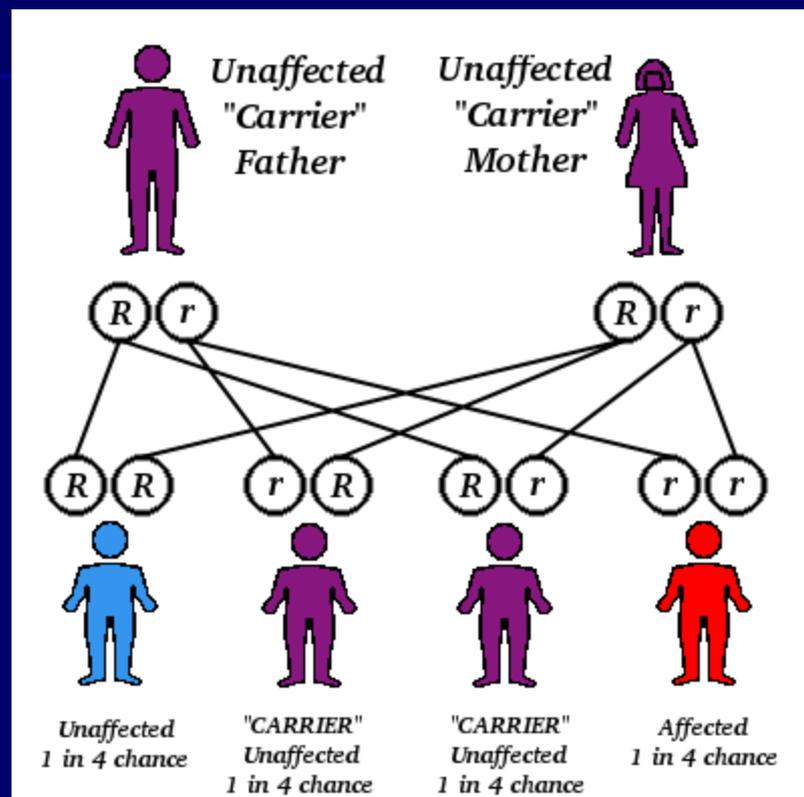


# QUESTIONS?

- [Diana.hu@tchealth.org](mailto:Diana.hu@tchealth.org)

# Inheritance of SCID

- Autosomal recessive
  - Mom and dad are asymptomatic carriers
  - 1:4 chance of infant being affected
  - 1:2 chance of other children as carriers
- Specific unique gene mutation found in Athabaskan population

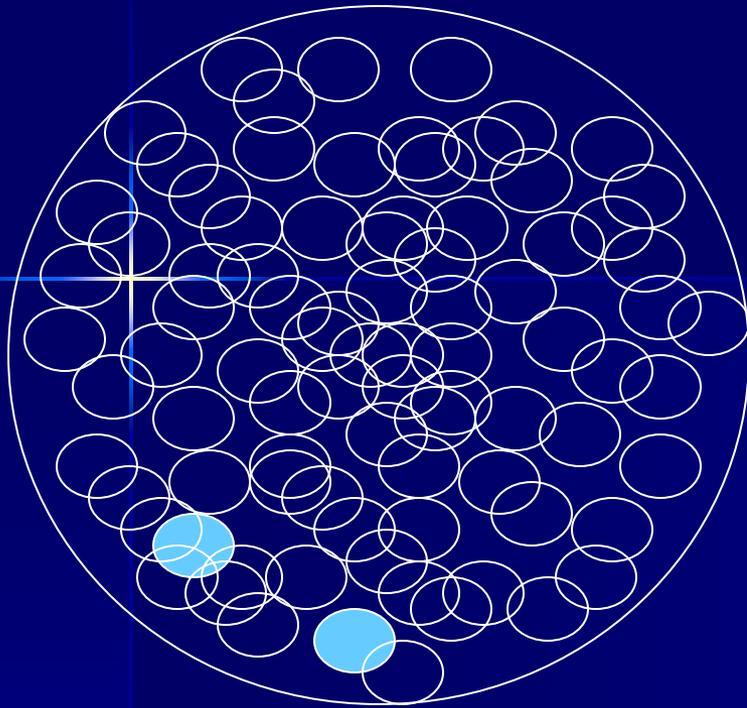


# Gene Mutation for SCID-A

- In a gene called *Artemis* located on Chromosome 10
  - Responsible for development of diversity of immunoglobulins and T-cell receptors in the immune system
  - May have effects on the ability of DNA to repair after damage
- Estimated carrier freq 1:30 western reservation Navajo

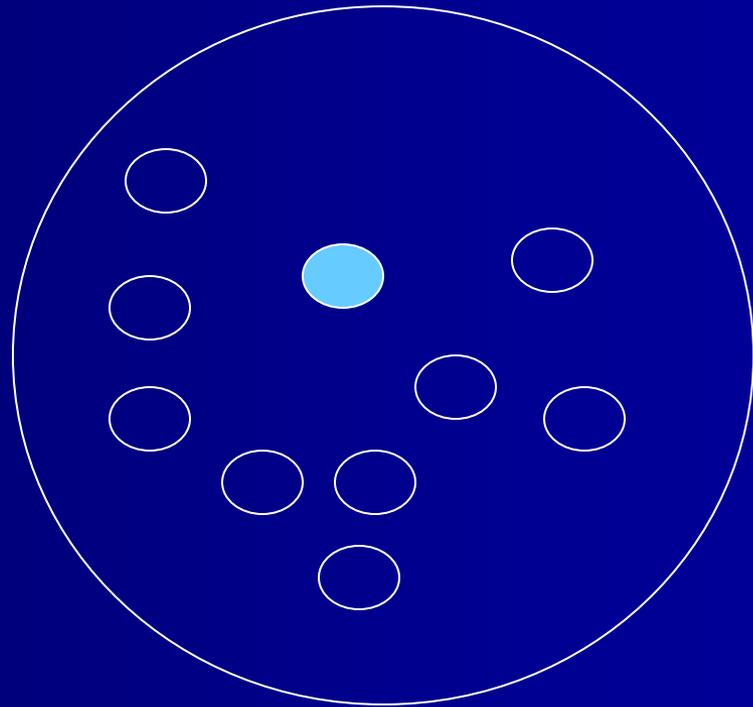
# Why is it higher in Athabascans?

- Founder effect -a gene rare in the general population occurs in a *small, isolated, rapidly expanding population* which leads to an *increased gene frequency* and increased frequency of disease in that population.



Initial gene  
frequency - 2:100

After population  
reduction: gene  
frequency - 1:10



# SCID-A –Navajo experience

- 31 Navajo children since 1978
  - 23 since 1987
- 1/8 long term survivors born between 1978-1987
  - Survivor diagnosed clinically at age 6 weeks with NOMA, transplanted age 3 months
  - Only 4/8 transplanted- others too ill at the time of diagnosis for transplant

# SCID-A— Navajo experience

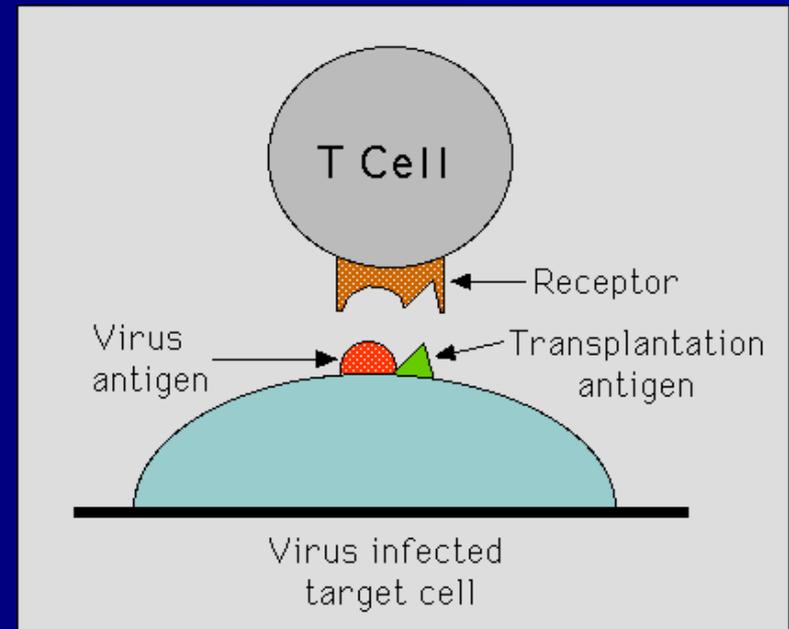
- Since 1987
  - 16/23 long term survivors
    - 22 transplanted UCSF, Duke, Sloan Kettering, Denver, PCH
    - 1 not transplanted due to severe infection at time of diagnosis
  - 5/6 children who died after transplant were identified after age 4 months
    - Presented with recurrent or persistent infection
    - 1/6 who was identified at birth died age 21 chronic lung disease

# SCID in Athabascans

- Also have had 2 families with other forms of SCID (not SCID-A)
  - 2 brothers with X linked
  - 1 female with T-B+ SCID
- *success of therapy correlated with age at transplant (< 2 months of age)*

# T cells

- Have specific binding receptors that are unique to a specific antigen that they will attack



# TRECs

- T cell receptor excision circle (TREC)
- Extra DNA that is snipped out when making the DNA sequence that codes for a unique receptor
  - Part of normal T cell maturation
  - Numbers of TRECs are a reflection of the population of recently formed T cells in the blood
- Cost ~\$6 per test

# Newborn screening test

- Uses a tiny amount of blood
  - About 9 microliters from two punches
- DNA is extracted from the blood sample
- TREC numbers are counted
  - $< 30$  copies is associated with very low T-cell numbers
    - Would be clinically verified with standard T-cell subsets and function tests. (flow cytometry)

# Newborn screening technology

