Genetic Disorders in Native American/Alaska Native Children

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I have no significant financial relationships with any product or commercial manufacturer to disclose

And I even still have a separate checking account from my husband….

Objectives

If I have done my job, you will all be able to

- recognize the unique spectrum of genetic illnesses in Native American populations
  - And understand the role American History plays in shaping inheritance
- describe the impact of newborn screening on the recognition and treatment of SCID, a genetic illness, in the Athabascan population
- recognize cultural differences that may affect acceptance of a genetic diagnosis in a Native American patient

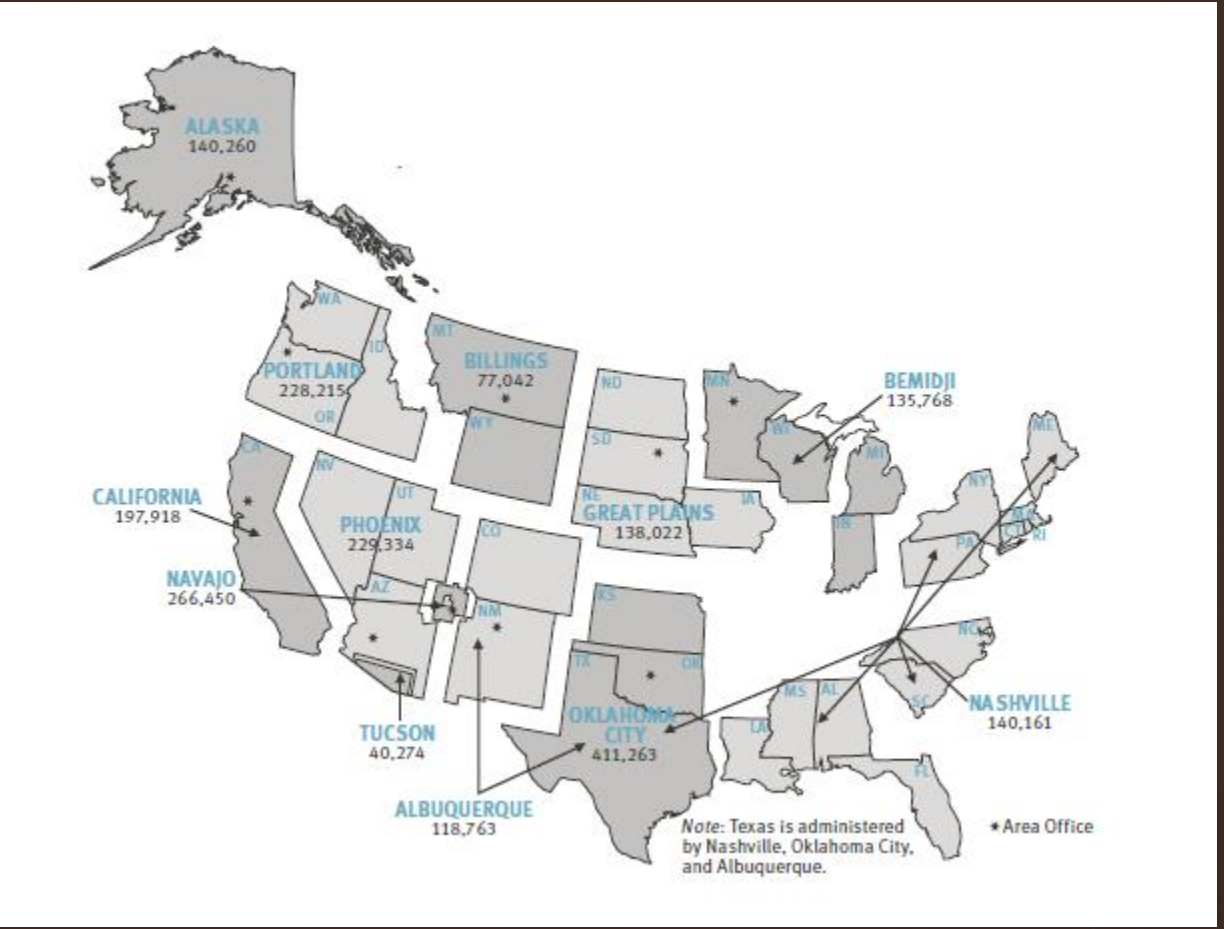
Disclaimers

- The focus of this presentation will be on Mendelian genetic disorders – mostly autosomal recessive- of higher prevalence in NA/AN populations
  - Especially those in the Athabascan (Navajo, Apache, some Alaska Native/First Nation tribes)
- I am not Native American but have worked with the Navajo/Hopi/San Juan Paiute population for over 30 years
- I am just a simple country doctor….

Native America: Nations within Nations

- 567 federally recognized tribes
  - 229 in Alaska
- All tribes are sovereign nations
- US federal government has a treaty obligation to sovereign Native American tribes that includes an obligation to provide health care
  - Government to government relationship

IHS population



Trends in Indian Health 2014 IHS DHHS

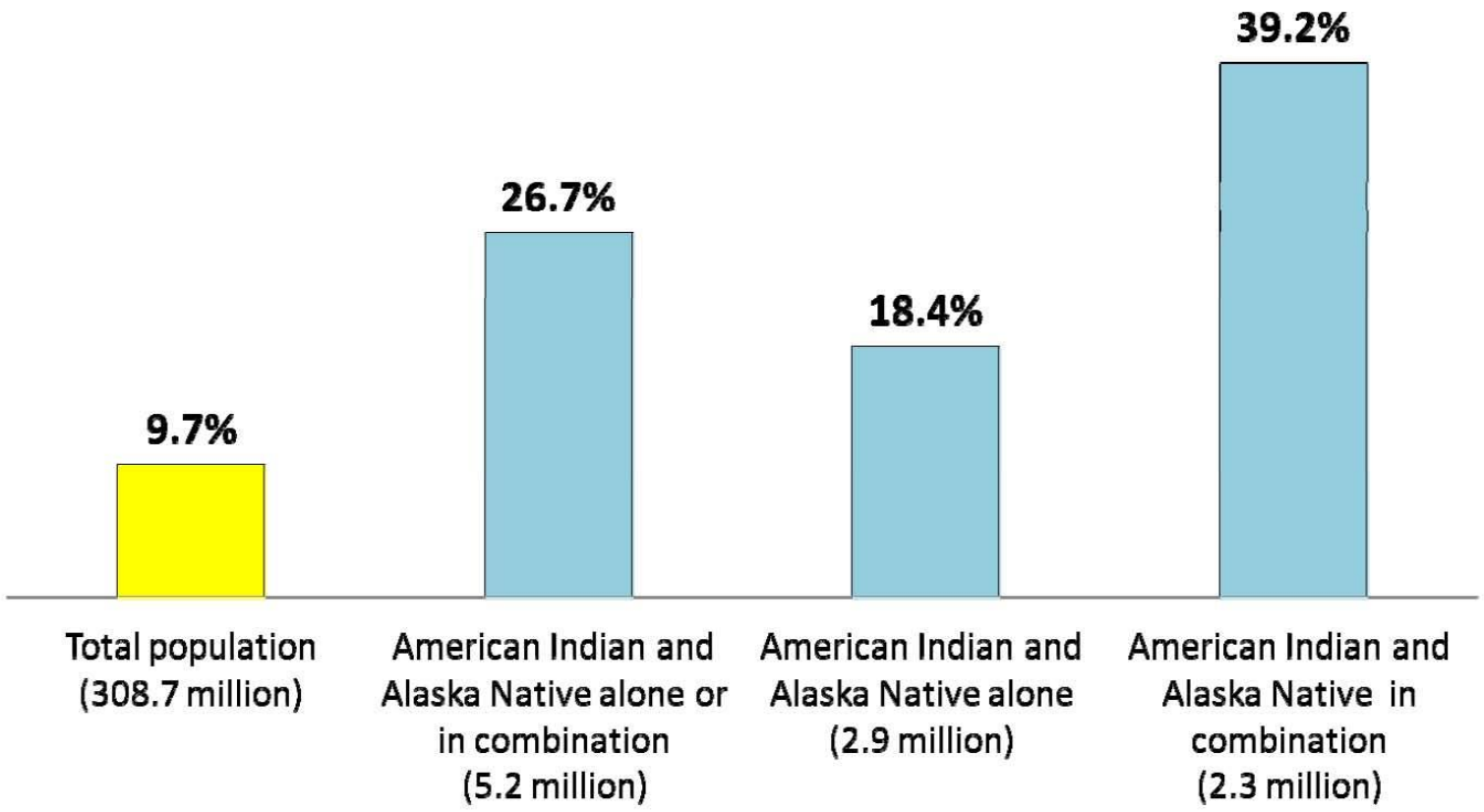
Native Americans in the US

- 2010 census
  - Single race: 2.9 million= 0.9% of US population
  - Mixed race or alone: 5.2 million=1.7% of US population
- Reservation lands/trust lands
  - 326 reservations in 33 states- 56.2 mill acres
    - Largest: Navajo Nation 27,000 sq miles, pop. 300,000
    - Smallest: Seminole Trust land, Fla 1.27 acres
- Over 50% of NA/AN live off reservations

Native American populations are:

- Younger
  - Median age 30.2y vs 37.8 all US
  - Birth rate 1.5x higher avg US
- Poorer
  - 29.2% of households below poverty level vs 15.9% all US
  - Highest unemployment
    - 13.1% males, 11.95 females
- Less likely to have a college degree
  - 14.1% vs 30.6% all US races
- diverse

Percent Increase of the American Indian and Alaska Native Population: 2000 to 2010



Sources: Census 2000 and 2010 Census

United States Census Bureau

Shared experiences

- Cultural preservation
  - Creation stories
- Tribal sovereignty
- Historical trauma
  - Forced relocations- the Long Walk, Trail of Tears
    - Population reductions-Founder effect
  - Boarding school experiences
  - Racism/stereotyping
- ACEs
  - Adverse childhood experiences
    - Effect on epigenetics

Shared experiences

- On reservation universal access to health care through the Indian Health Service I/T/U system
  - “socialized medicine”
  - Variable services depending on location/staffing/governance
- Off reservation – variable access to subsidized health services
  - Some tribes have partnerships with local or national health care organizations to provide care to their members
- Changing relationships between tribes and research community
  - Tribes setting their research agendas

Unique Genetic Diseases of Navajo/Athabascan Children

- Severe Combined Immune Deficiency Syndrome-Athabascan type (SCID-A)
- Athabascan Brain Stem Dysgenesis
- Navajo NeuroHepatopathy
- Poikiloderma with Neutropenia, Clericuzio type

Genetic diseases with increased incidence in the Navajo

- Metachromatic Leukodystrophy
- Xeroderma Pigmentosa
- Oculocutaneous Albinism2-
- Oral Facial Digital syndrome IX with microcephaly
- Microvillus Inclusion Disease
- Congenital Adrenal Hyperplasia (21-OH deficiency)

Genetic diseases of increased incidence in other Tribes

- Oculocutaneous albinism- Hopi, Zuni, Jemez, Laguna, San Juan
- Cystic Fibrosis- Zuni
- Scleroderma- Oklahoma Choctaw
- Glutaric Aciduria type 1 - Cree

Genetic diseases of increased incidence in Alaska Natives

- Carnitine Palmitoyl Transferase Deficiency- Type 1A (CPT-1A def)- coastal Alaska natives, First Nations in Canada, Siberians
- Congenital adrenal hyperplasia -21 OH deficiency – Yupik
- Metchromatic Leukodystrophy- Western Alaska Athabascan
- Congenital Sucrase-Isomaltase Deficiency- Alaska Natives/Greenland and Canadian Inuit
- Kuskokwim syndrome (arthrogryposis like contractures) – Yupik in YK delta
- (Septo-optic dysplasia?)

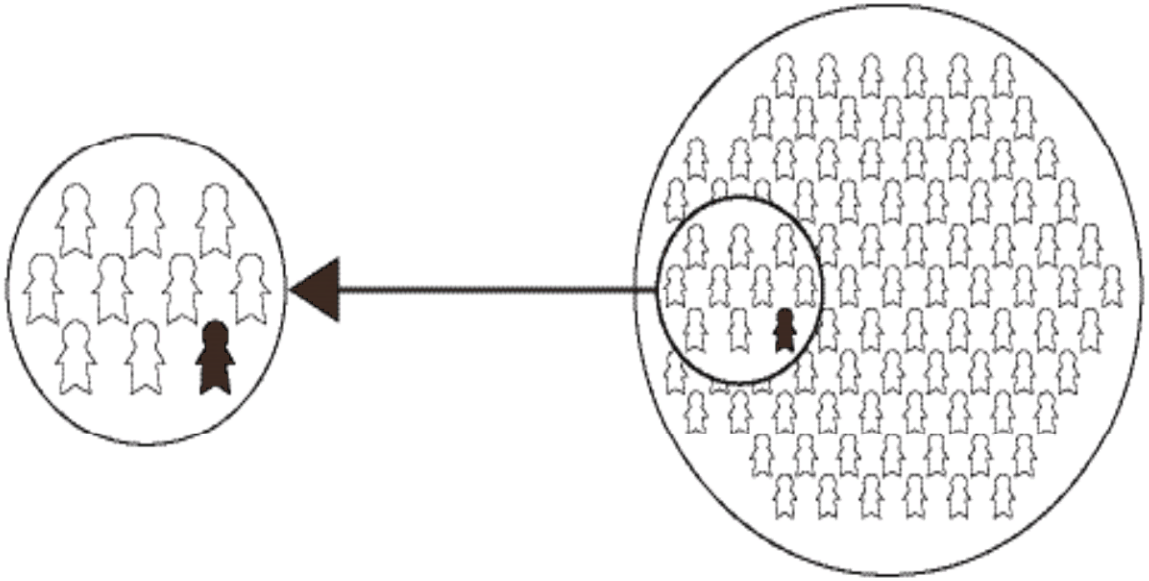
Genetic illnesses and Native Americans

- Why is this the case?
- Is it improved case finding because of the IHS system?
- All persons carry many mutations in their genome
  - Average 7 mutations leading to potential autosomal recessive disease
    - But most of us do not have children with people who have the same genetic mutations because of genetic variability
- Why would this be more common in Native populations?

Founder Effect

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

THE FOUNDER EFFECT



New Gene Frequency
1/10

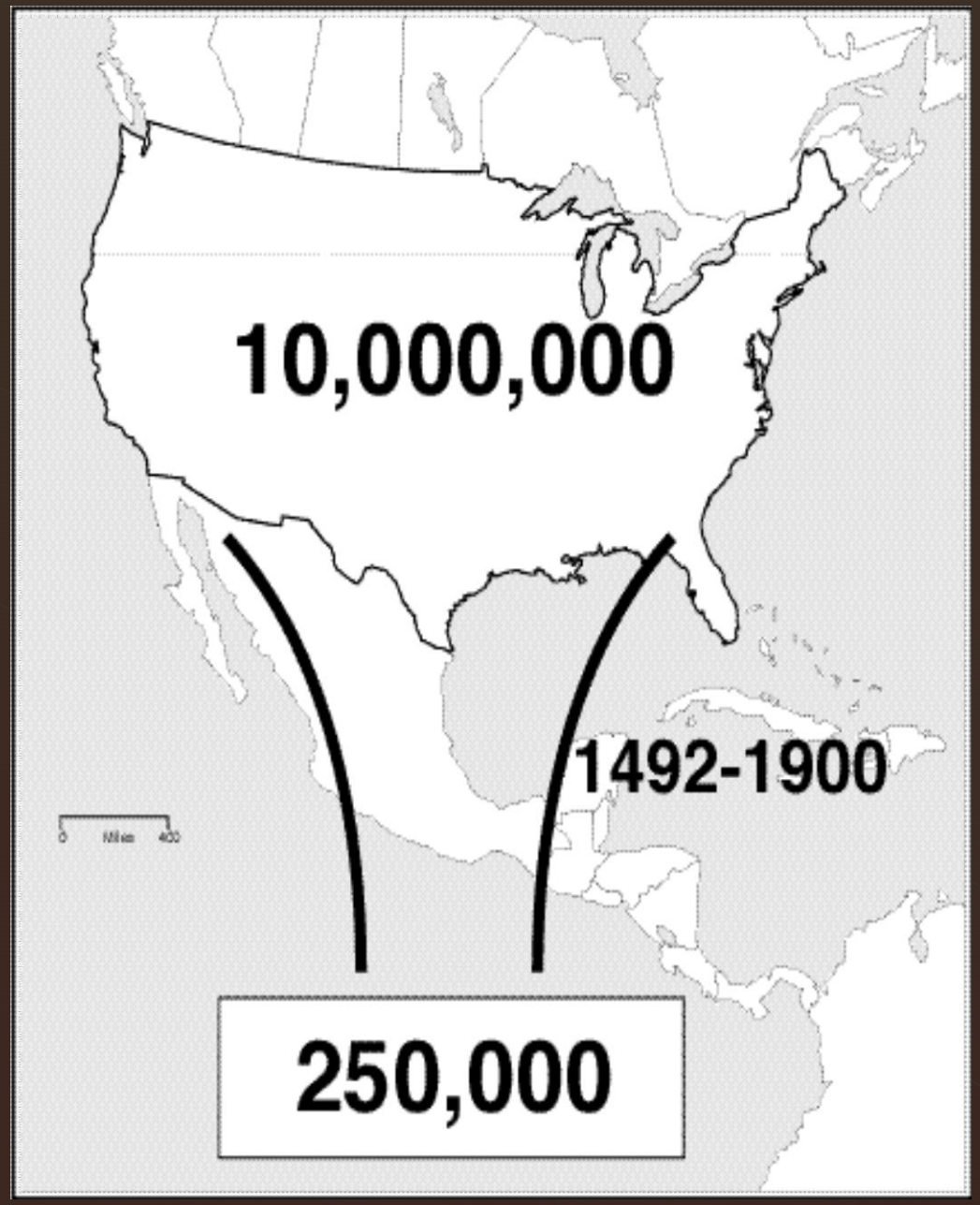
Original Gene Frequency
1/100

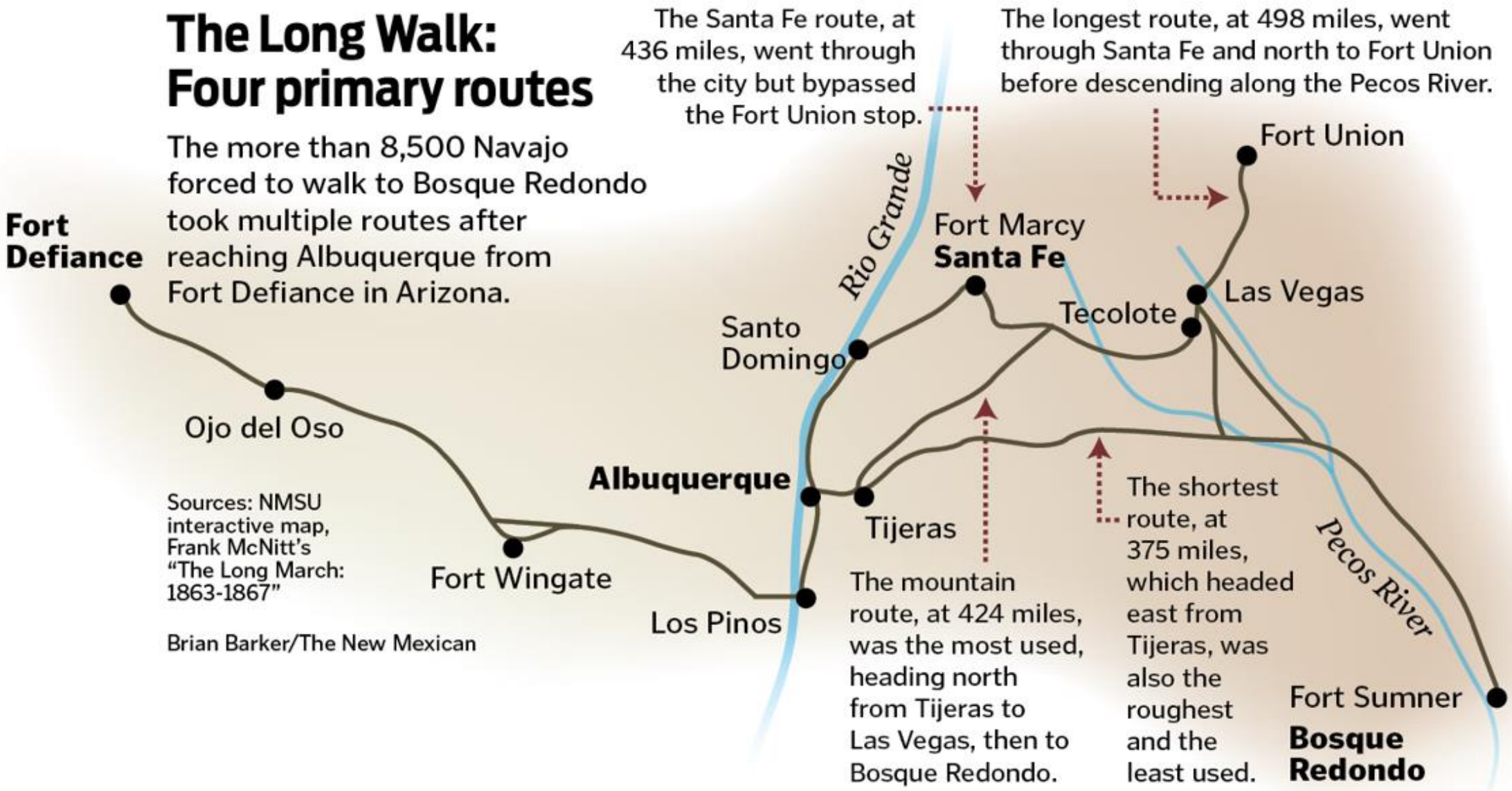
Examples of the Founder effect

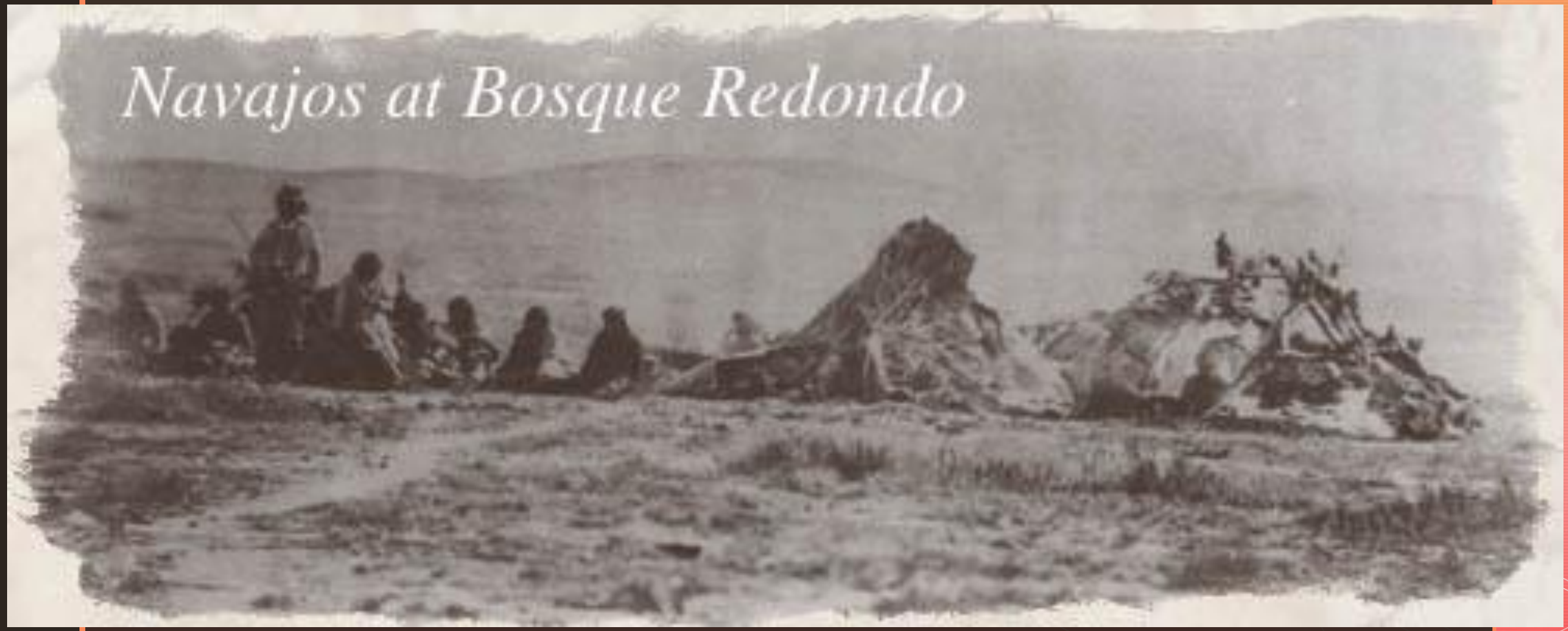
- Religion - The Hutterites and the Amish
- Ethnicity - French Canadians and Ashkenazi Jews
- Geography - island populations- Iceland

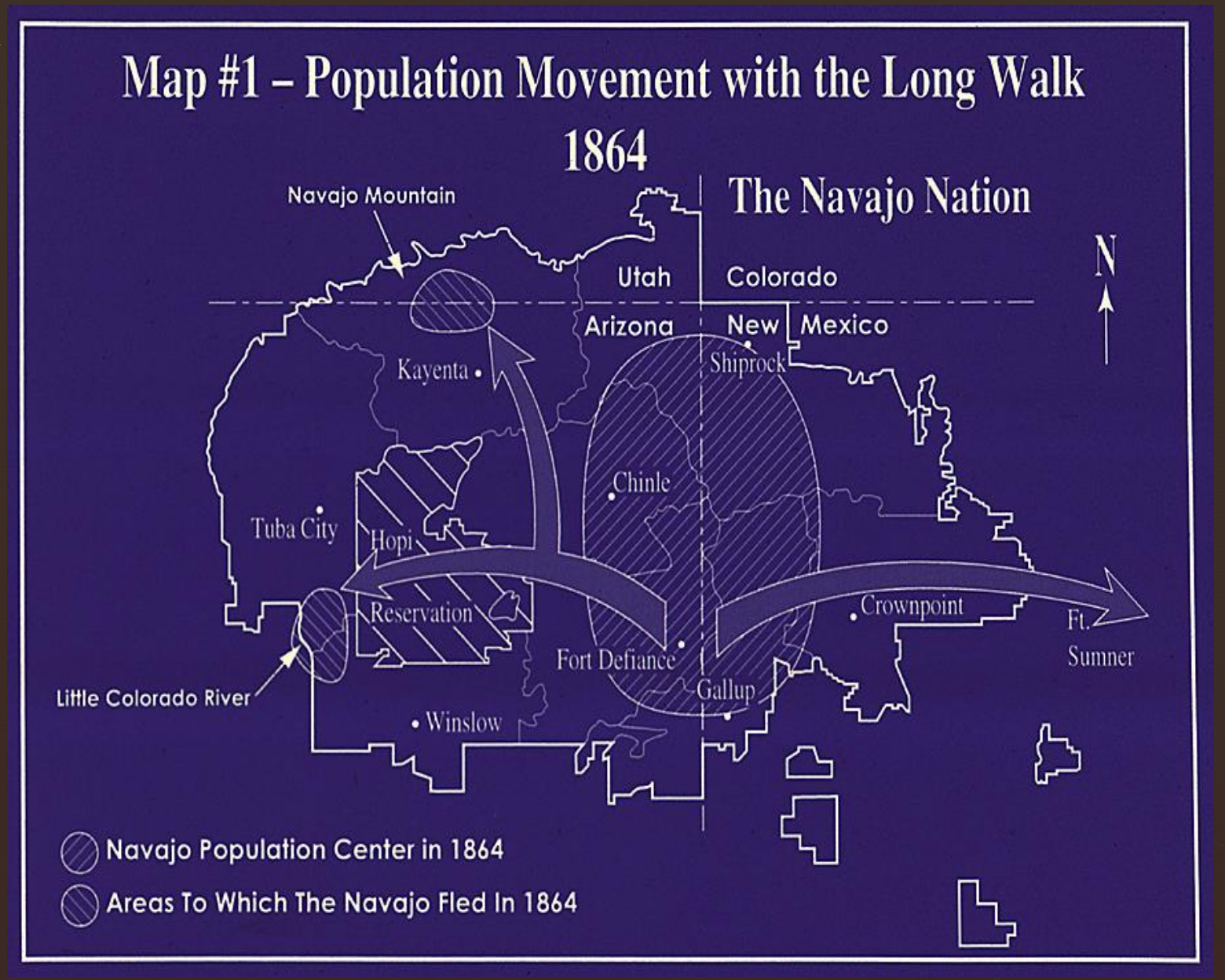
First Contact Population Reductions

- Disease- smallpox, influenza, cholera, measles
- Smallpox
  - Florida- 700,000 in 1500s reduced to 2000 by 1700
  - Southeast total reduction to <5000 by 1700
  - Huron tribe reduction by 50% in 1634 to 9000
  - Lakota 1700s “the great dying”
  - Estimated .5 to 1.5 million died from smallpox
- French and Indian Wars- British used smallpox as ”biologic warfare” against Native Americans
  - Smallpox infested blankets to the Delaware tribe


10,000,000
1492-1900
250,000


The Long Walk:
Four primary routes
The more than 8,500 Navajo forced to walk to Bosque Redondo took multiple routes after reaching Albuquerque from Fort Defiance in Arizona.
The Santa Fe route, at 436 miles, went through the city but bypassed the Fort Union stop.
The longest route, at 498 miles, went through Santa Fe and north to Fort Union before descending along the Pecos River.
Fort Defiance
Ojo del Oso
Fort Wingate
Los Pinos
Albuquerque
Santo Domingo
Rio Grande
Fort Marcy
Santa Fe
Tecolote
Las Vegas
Fort Union
Tijeras
Pecos River
Fort Sumner
Bosque Redondo
The mountain route, at 424 miles, was the most used, heading north from Tijeras to Las Vegas, then to Bosque Redondo.
The shortest route, at 375 miles, which headed east from Tijeras, was also the roughest and the least used.
Sources: NMSU interactive map, Frank McNitt's "The Long March: 1863-1867"
Brian Barker/The New Mexican


Navajos at Bosque Redondo


Map #1 – Population Movement with the Long Walk
1864
The Navajo Nation
Navajo Mountain
Utah
Colorado
Arizona
New Mexico
N
Shiprock
Kayenta
Chinle
Tuba City
Hopi
Reservation
Crownpoint
Ft. Sumner
Fort Defiance
Gallup
Little Colorado River
Winslow
Navajo Population Center in 1864
Areas To Which The Navajo Fled In 1864

Conditions Favoring the Founder Effect in the Navajo

- Population reduction during the Long Walk
- Geographic Isolation
- Rapid population increase
  - double fertility rate
  - Navajo population increased 30 fold in 5-6 generations vs. 5 fold for U.S.

Indian Removal Act -1830

- Trail of Tears- Choctaw, Cherokee, Muskogee (Creek)
  - Seminole
  - Chickasaw
  - Relocation to Oklahoma
- Sauk and Fox – Illinois to Iowa
- Potawatami- Great Lakes to Kansas to Oklahoma
- Chiracuhua Apache- out of Arizona

Unique Genetic Diseases of Navajo/Athabascan Children

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- Navajo NeuroHepatopathy
- Poikiloderma with Neutropenia, Clericuzio type

SCID-A

- T and B lymphocytes are absent
  - Unable to mount immune response directly to bacteria, viruses and fungi
  - Unable to make immunoglobulin
    - To fight infection
    - To respond to immunizations
  - No immunologic memory

SCID-A

- now known to occur in 4 Apache tribes, Dene’ (Northwest Canadian Athabascan tribe)
- unique gene mutation found in *Artemis (DCLRE1C)* gene on 10p
  - C->A change in Exon 8 - nonsense mutation inhibits V(D)J recombination in receptor formation
- *Artemis* has a role in DNA repair/sensitivity to ionizing radiation, immune system ontogeny/diversity

SCID-A –Navajo experience

- Incidence 1:2000 western Navajo
- 36 Navajo children since 1978
  - 28 since 1987
- 4 detected by newborn TREC screening
  - 1 missed because born off reservation before state wide screening implemented
- Long term survival correlated with diagnosis before 2 mos of age
- Treatment- HSCT
  - B cell deficiency post transplant more common

TREC screening

- T cell receptor excision circles
- Extra DNA not needed by the t cell
- No t cells= no TRECs
- Not a genetic test
  - 3.1 mill newborns Sensitivity 100% for SCID
  - PPV varied based on cut off for TREC level- 20 vs 40 0.8-11%
  - Two other phenotypes/genotypes of SCID found in Navajo/Apache populations- would be missed by genetic test, but found on TREC

WHO Criteria Screening

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

Athabascan Brainstem Dysgenesis

- Horizontal Gaze Palsy
  - Duane syndrome- absence of the abducens (CN VI) brain stem nucleus
- Central Hypoventilation
- Sensorineural Deafness-
  - early diagnosis with universal newborn hearing screening
- Developmental Delay

Athabascan Brain Stem Dysgenesis

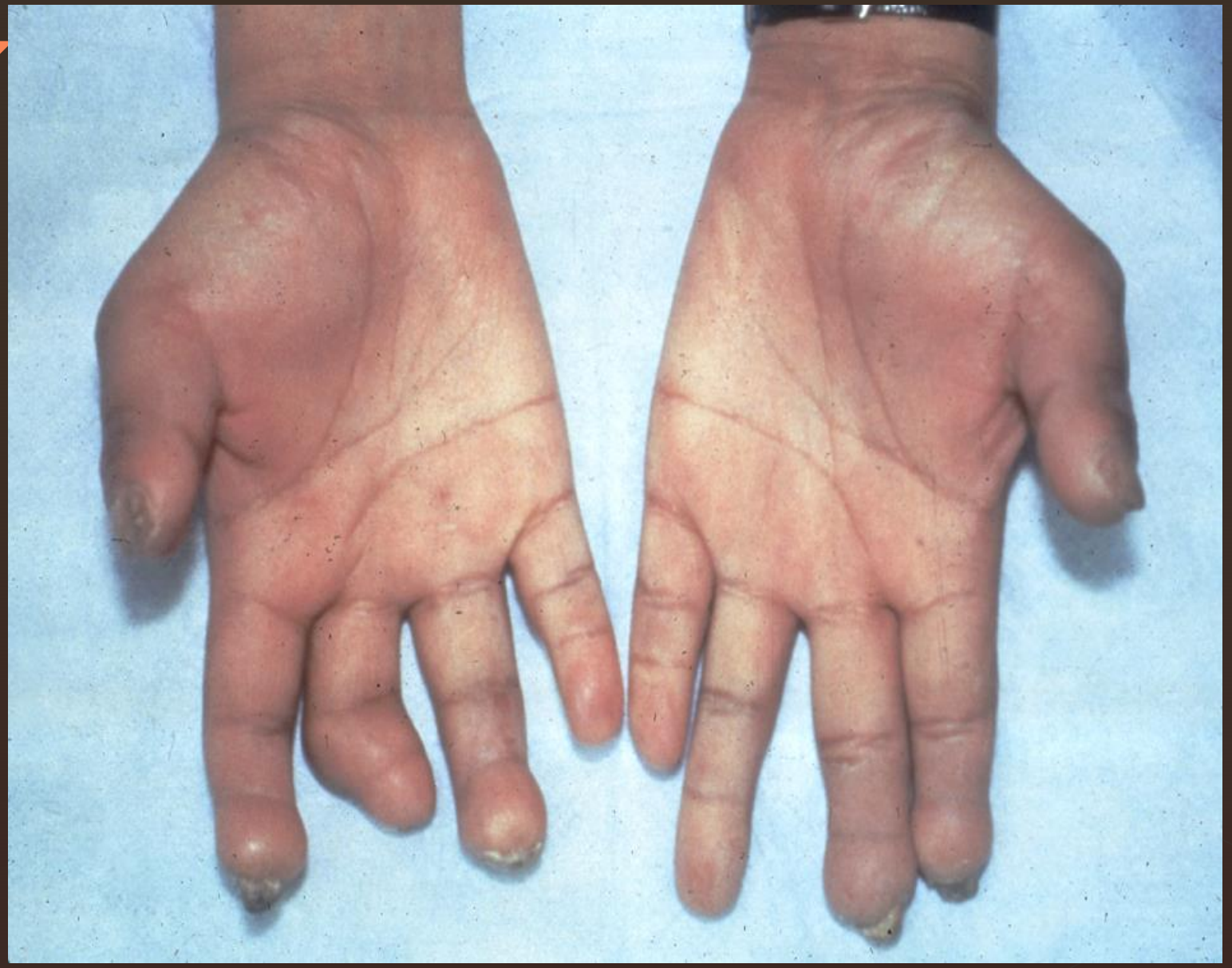
- Seizure Disorder
- Cardiac Outflow Tract Anomalies
  - TOF, aberrant subclavian arteries, double aortic arch, aortic coarctation
- Facial weakness
- Vocal cord paralysis

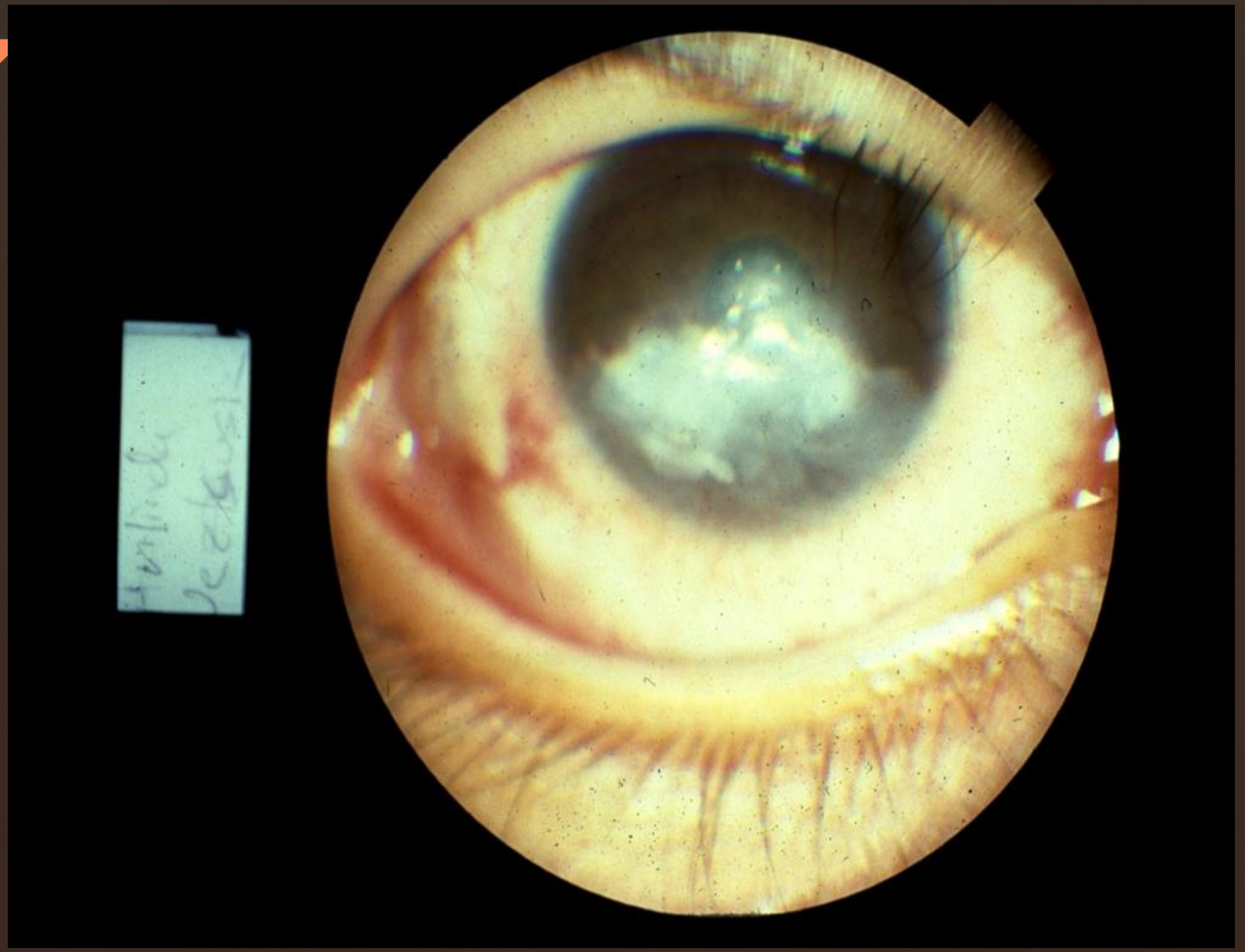
Athabascan Brain Stem Dysgenesis

- Unique homozygous HOXA1 mutation: 7p15 C->T mutation in exon 1 in 5 probands, heterozygous in 4 parents
  - Similarities with Bosley-Salih-Alorainy Syndrome (BSAS) in Saudi Arabian/Turkish patients with Duane syndrome, sensorineural deafness, developmental delay, autism spectrum disorder, abnormal internal carotid arteries- 84 C-G mutation in Exon 1 .
- 1st human disease associated with homozygous mutation in HOX genes.

Navajo NeuroHepatopathy Diagnostic Criteria

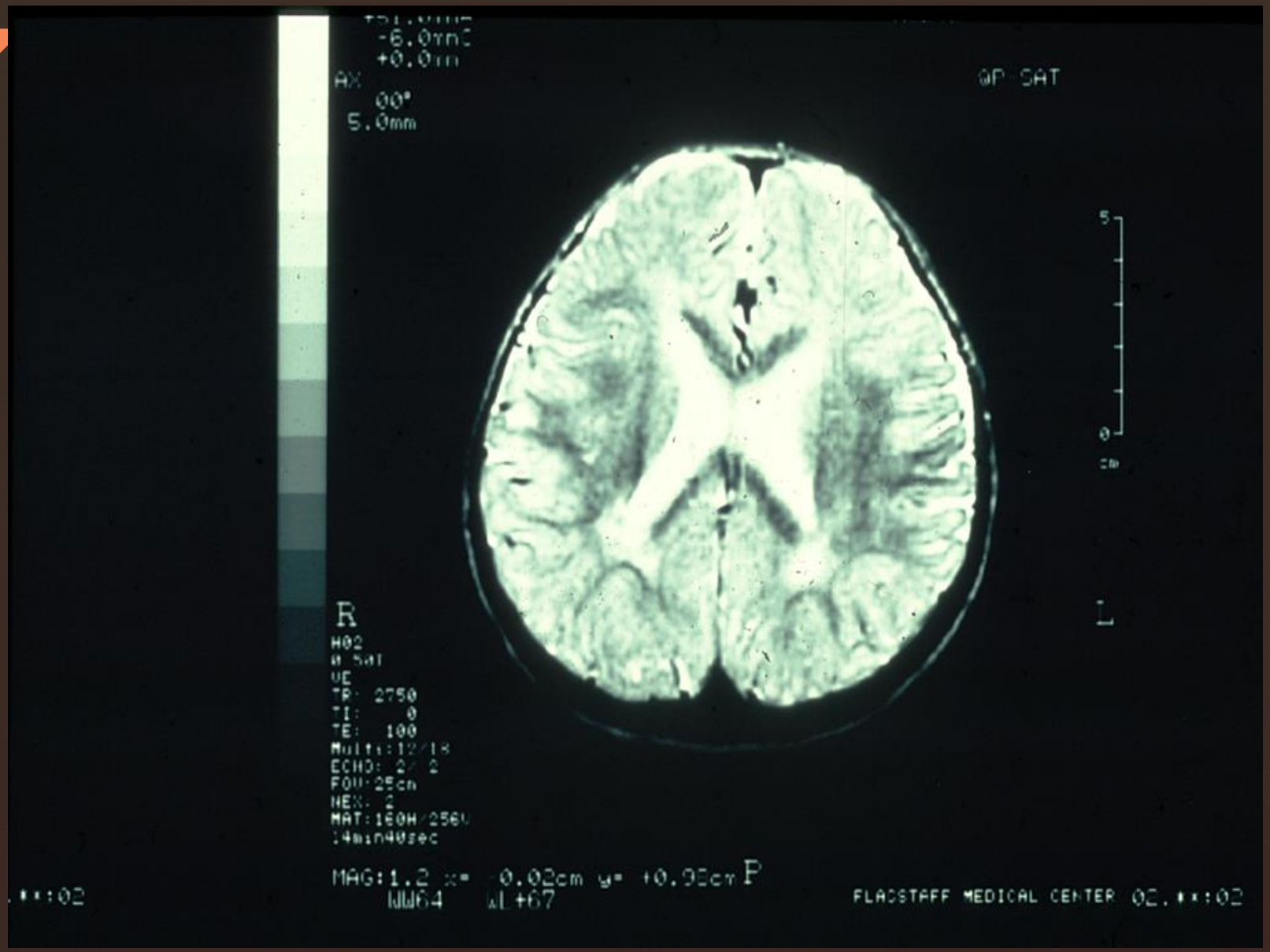
- Clinical presentation
  - Sensory Neuropathy
  - Motor Neuropathy
  - Corneal Anesthesia
  - Liver Disease
  - Metabolic or infectious disease derangement
  - CNS demyelination on radiologic imaging
- 4/6 or 3/6 and sibling with NN





Navajo NeuroHepatopathy

- Sural Nerve Biopsy in 12/12
- Loss of myelinated fibers
- degeneration and regeneration of nonmyelinated axons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TI: 0
TE: 100
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WW64 WL+67
FLAGSTAFF MEDICAL CENTER

Liver Disease in Navajo NeuroHepatopathy

- neonatal hepatitis
- fulminant liver failure in childhood
- cryptogenic cirrhosis
- hepatocellular carcinoma
- common feature - elevated GGT

Presentations of Navajo NeuroHepatopathy

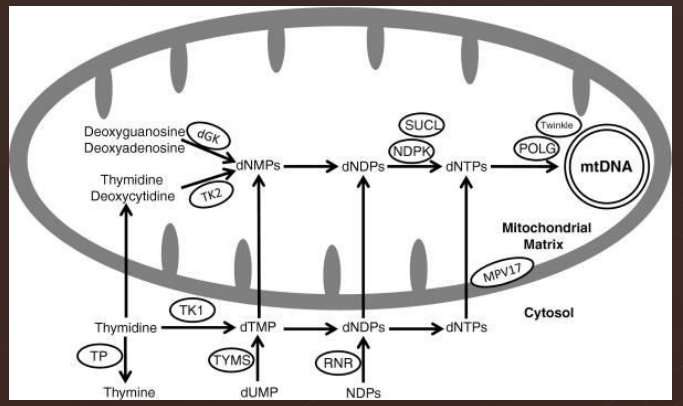
- Infantile- fatal liver disease in first year of life
- Early Childhood- gross motor developmental delay, some eye disease, acute liver failure with viral illness
- Classic- neuropathic findings developing over 1st decade. Liver disease minor.
- Mixed- neuropathic findings increase with age, chronic cirrhosis with varices or hepatocellular carcinoma in second decade

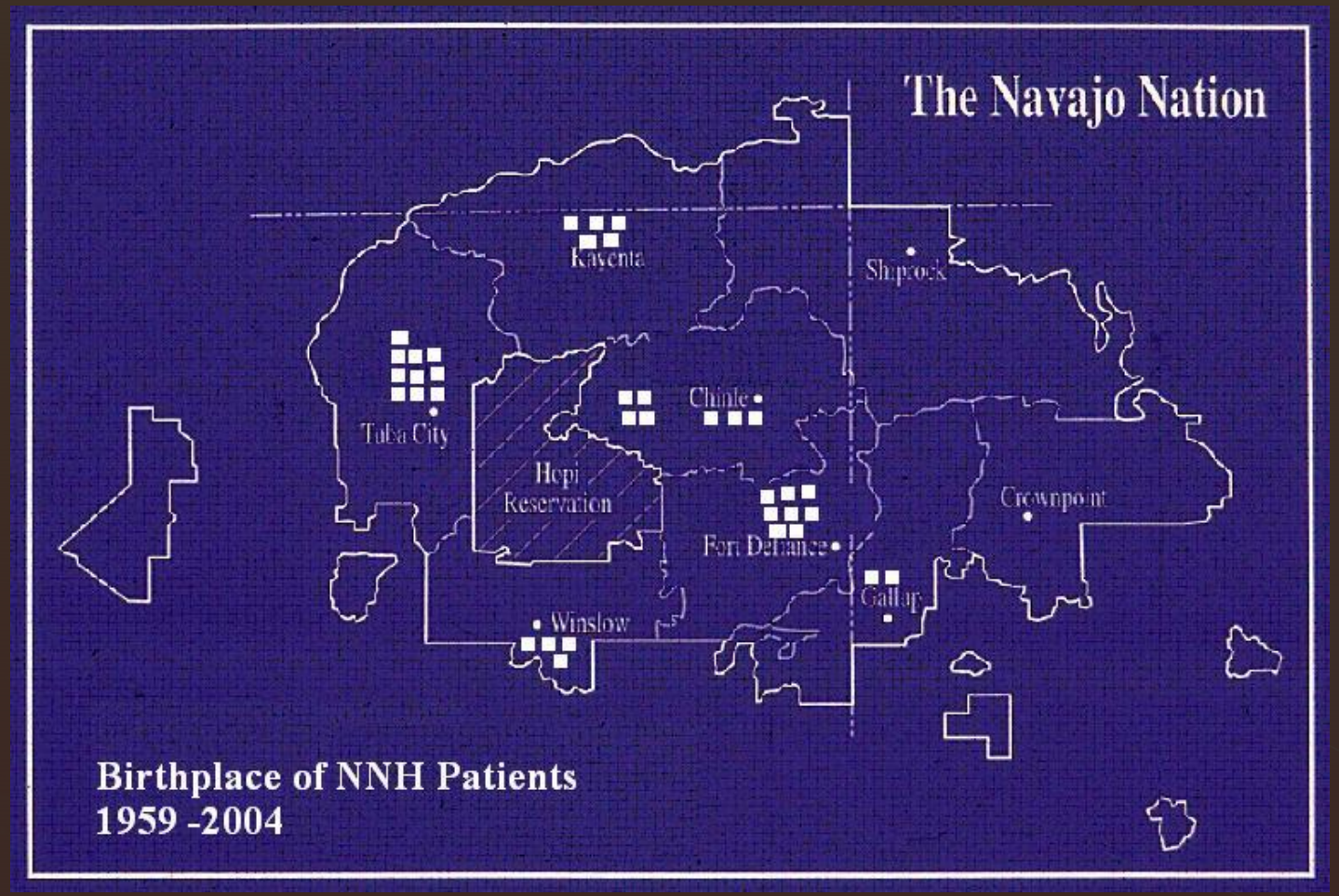
Navajo NeuroHepatopathy

- Mitochondrial depletion syndrome
- A->G mutation in MPV17 gene chromosome 2p24
  - Italian and Moroccan families with similar phenotype found to have homozygous and compound heterozygous mutations in MPV17

Mitochondrial depletion syndromes

- Nuclear DNA that codes for mitochondrial function
  - Maintenance of mtNTP or mtDNA pool
  - Autosomal recessive rather than maternal inheritance
  - Heterogeneous disorders
    - Brain, liver




The Navajo Nation
Kayenta
Shiprock
Tuba City
Chinle
Hopi
Reservation
Crownpoint
Fort Defiance
Gallup
Winslow
Birthplace of NNH Patients
1959 -2004

LA Times

- **“Oases in Navajo desert contained 'a witch's brew’”**
  - **Rain-filled uranium pits provided drinking water for people and animals. Then a mysterious wasting illness emerged.**
    - By Judy Pasternak, Times Staff Writer
      November 20, 2006

Founder Effect or Toxic Effect?

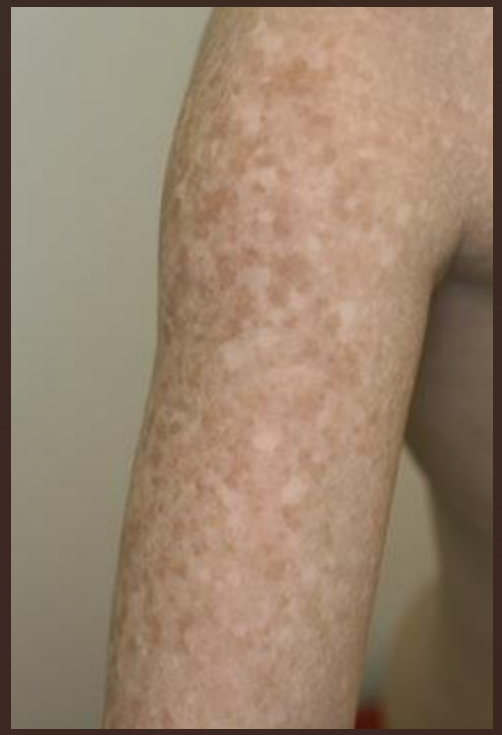
- Genotype evidence is compelling but does this explain the different phenotypes that are seen ?
- Uranium exposure was possible in some of the cases, but not conclusively proven
- Is pre or post natal uranium exposure a cofactor that unmasks a genetic predisposition?

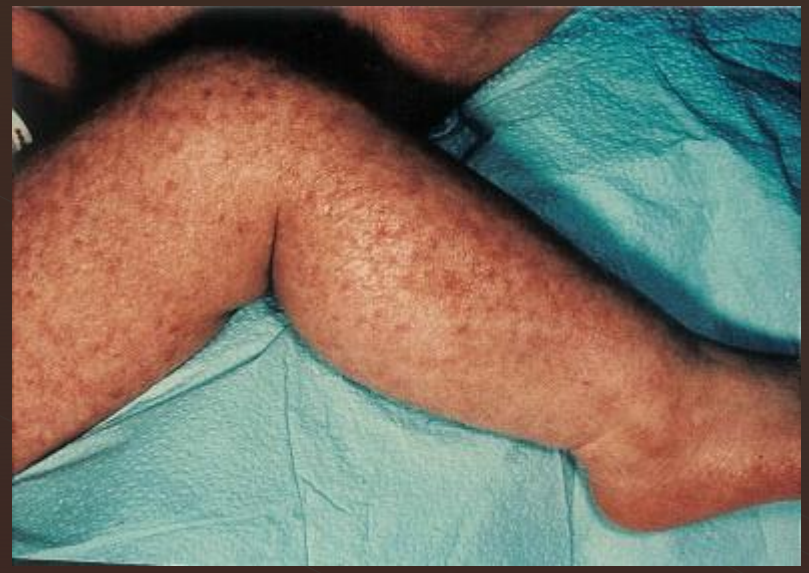
Poikiloderma with Neutropenia, Clericuzio type

- Skin looks normal initially
  - Inflammatory eczematous rash ages 6-12 mos
  - Post inflammatory hypo-hyperpigmentation
  - Nail dystrophy, plamar keratosis
  - Skin nodules
- Non cyclic neutropenia
  - Recurrent sinopulmonary infections
  - Bronchiectasis
- GERD
- Asthma
- Short stature
- Higher risk myelodysplastic syndrome/AML

Poikiloderma with Neutropenia

- C16orf57 (USB1) chromosome 16q21 unique deletion exon 4
  - Other mutations in same gene in other ethnicities- Turkish, Moroccan families with similar skin disease



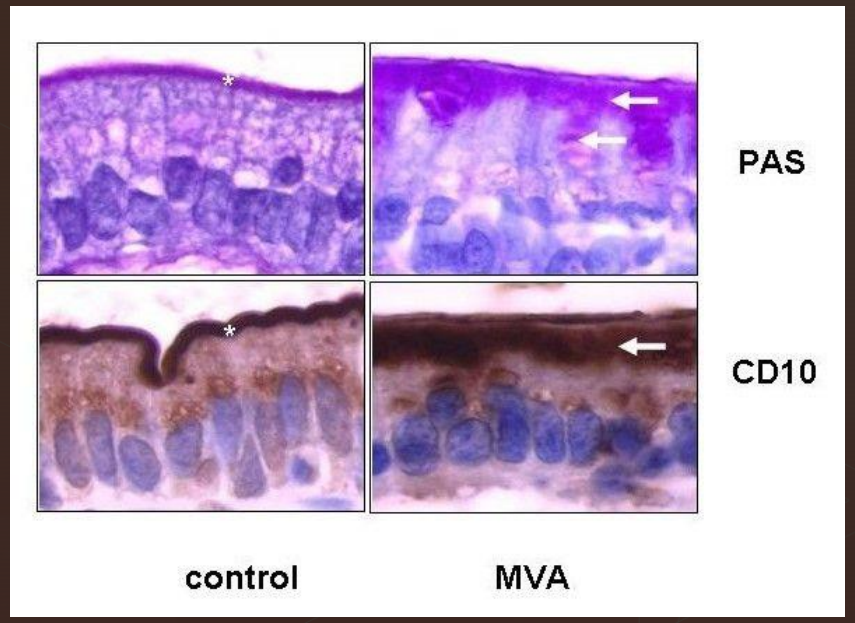


Metachromatic leukodystrophy

- Late infantile form-
  - Loss of developmental milestones
  - Progressive neurologic degeneration, seizures, spasticity, aspiration, respiratory insufficiency
- Deficiency in enzyme arylsulfatase A that degrades sulfatides
  - Sulfatides are toxic to myelin
- Unique G– A mutation found in intron 4 chr 22q13
  - Same gene mutation in Southern Alaskan Athabascan NA
- 14 different genotypes known associated with different phenotypes- seen in all ethnicities

Microvillus inclusion disease

- Failure to form microvilli due to changes in cell polarity in the intestinal wall
- Chronic secretory diarrhea- TPN dependent
- Missense Mutation in MYO5B chromosome 18q21



Oculocutaneous Albinism 2 (OCA2)

- Occurs in many Pueblo tribes, increased in Navajos not seen in Apaches
  - Navajo incidence 1:2000
- Unique 122.5 kilobase deletion in P gene unique to Navajos
  - Carrier frequency 4.5%
- Deletion NOT seen in normally pigmented Apaches or any other affected NA

Congenital Adrenal Hyperplasia

- Incidence 3x higher in AK, 13x higher in Yupik
  - 1:600 live births Yupik Eskimos
  - 1:16000 general population
- Newborn screen measures 17-OH progesterone levels
- Mutation CYP21A2 Chr 6p21 (over 100 mutations found)
  - Yupik homozygous for large intron 2 del A/C->G mutation
  - Other NA homozygous 40%, heteroozygous other mutations/phenotypes

Heritable Diseases- Incidence

	Western Navajo	U.S.
MLD	1:3000	1:40,000
SCID-A	1:2000	1:100,000
MVID	1:2000	1:1,000,000
OCA-2	1:2000	1:36,000
Nav Neuropathy	1:1600	-----
Brainstem Dys	1:2600	-----
Poikiloderma with Neutropenia	?	-----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Cultural Humility/Competence

- Sovereignty
  - Ownership of data
  - Ownership of genetic material
  - Setting the research agenda

Cultural Humility /Competence

- Identity
  - Cultural relationships to blood and tissues as self/spirit
  - Identity as Native American
    - Individual ancestry
    - Tribal migrations/homelands
      - Creation stories
- Trust
  - Racism/stereotypes- “inbreeding”
  - Health care beliefs

Beneficence

- The ethical principle that the welfare of the participant is the goal- to favor the well being and interest of the client/patient/research participant
- Are there cultural differences in defining harm or risk of negative consequences?

Summary

- Native American/Alaska Native children have a higher risk for unique and unusual genetic illnesses
  - The founder effect may play a role
- There are unique opportunities for genetic information to shape the care of NA /AN patients
  - Early identification of disease
  - Newborn screening , treatment modification, gene therapy
- Awareness of cultural differences and special considerations must be taken when working with tribes and tribal members


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