MOUNT SINAI CENTER FOR JEWISH GENETIC DISEASES

Department of Genetics & Genomic Sciences

Mount Sinai School of Medicine of New York University

TAY-SACHS DISEASE: LESSONS FROM ETHNIC-SPECIFIC CARRIER SCREENING

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DISEASES SCREENED IN CERTAIN POPULATIONS

Disease	Ethnic Group	Carrier Freq.	At-Risk Couple Freq.	Disease Incidence Newborns
Sickle cell	African-Americans	1/12	1/145	1/575
Gaucher	Ashkenazi Jews	1/15	1/225	1/900
Tay-Sachs	Ashkenazi Jews	1/30	1/900	1/3600
Cystic Fibrosis	Northern Europeans	1/24	1/576	1/2300
β-Thalassemia	Greeks, Italians	1/30	1/900	1/3600
α-Thalassemia	Chinese, SE Asians	1/25	1/625	1/2500

INHERITED DISEASES IN ASHKENAZI JEWS

Disease	Percent Jewish	Estimated Incidence	
		Jewish	General
Tay-Sachs	**95**	**1 : 3600**	**1 : 300,000**
Gaucher Type 1	80	1 : 900	very rare
Canavan	90	1 13,000	very rare
Niemann-Pick Types A & B	80	1 : 30,000	1 : 100,000
Familial Dysautonomia	99	1 : 3600	very rare
Essential Pentosuria	99	1 : 2500	very rare
Factor XI Deficiency	90	1 : 200	1 : 500
Maple Syrup Urine Disease	?	1 : 27,600	1 : 290,000
Fanconi Anemia Group C	95	1 : 32,000	rare
Torsion Dystonia	80	1 : 40,000	?
Bloom Syndrome	60	1 : 46,000	very rare
Mucolipidosis IV	>80	1 : 62,500	?
Glycogen Storage 1a	?	1 : 67,500	1 : 100,000

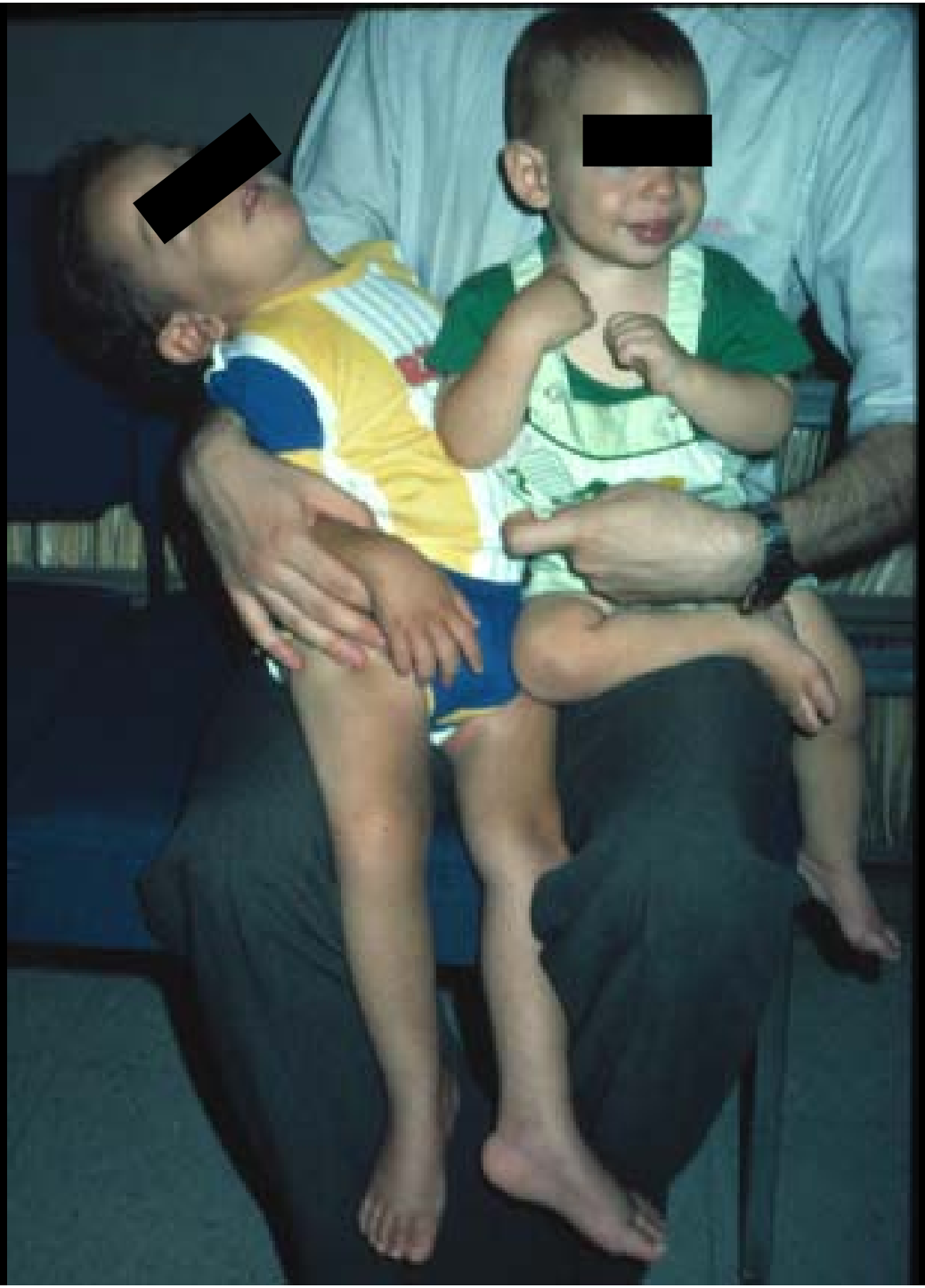
INHERITED DISEASES IN JEWISH ETHNIC GROUPS

Disease	Ashkenazi	Sephardi	Oriental		
			Yemeni	Iraqi/Kurdish	Iranian
	Gene Frequency				
Tay-Sachs Disease	.033	rare	-	-	-
Gaucher Disease	.067	rare	-	-	-
Pentosuria	.020	-	-	-	-
Familial Dysautonomia	.030	-	-	-	-
Familial Mediterranean Fever	rare	.04-.02	-	.01	-
Phenylketonuria	-	rare	.015	rare	<.01
α-Thalassemia	-	-	.14-.04	.08-.01	-
β-Thalassemia	rare	rare	rare	.08-.01	.01
Dubin-Johnson Syndrome	rare	rare	-	rare	.03

TAY - SACHS DISEASE

A Fatal Degenerative Disease of the Central Nervous System

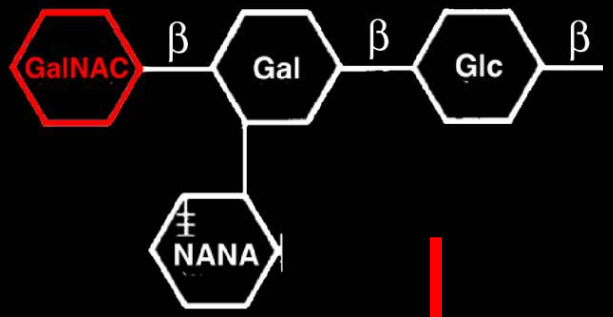
- Onset of Symptoms ~ 4-8 Months:
  - Progressive Mental and Motor Degeneration
  - "Cherry-Red" Macular Degeneration: Blindness; Hyperacusis
  - Progressive Muscular Weakness → Paralysis
  - Uncontrollable Seizures
- Autosomal Recessive Inheritance
- Jewish Predilection (95+%)
- Death ~ 2-5 Years of Life
- No Treatment Available



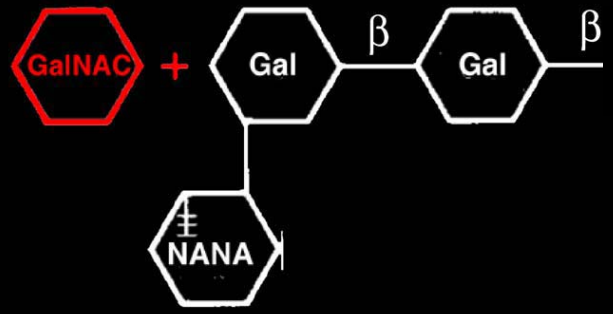
METABOLIC DEFECT IN TAY-SACHS DISEASE

Okada and O'Brien. *Science* 165:698-700, 1968

GM2 GANGLIOSIDE



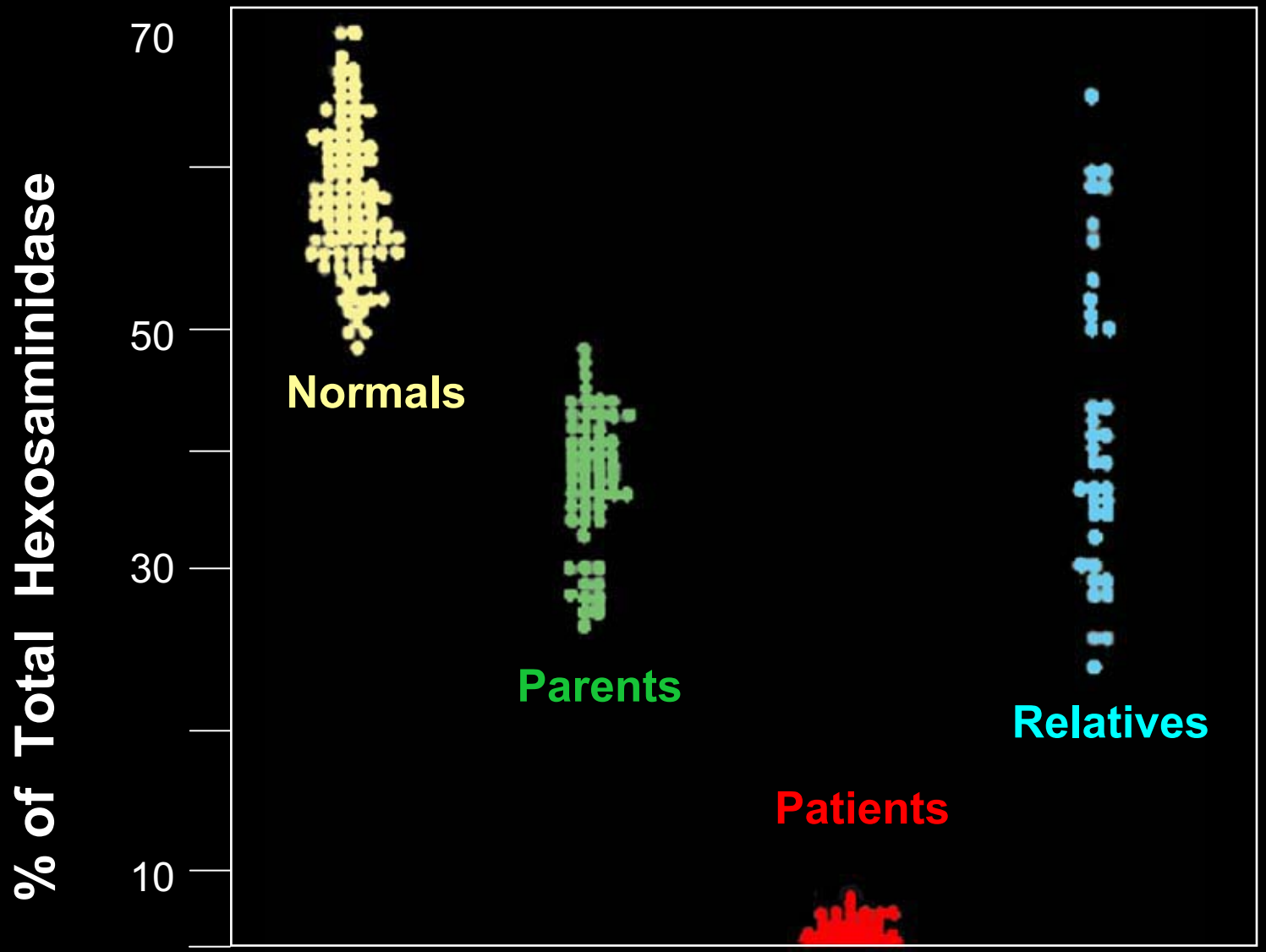
β-Hexosaminidase A



GM3 GANGLIOSIDE

SERUM β-HEXOSAMINIDASE A ACTIVITY

O'Brien et al. *N Engl J Med* 283:15-20, 1970



MUTATIONS CAUSING TAY-SACHS DISEASE IN THE ASHKENAZI JEWISH POPULATION

Mutation	Frequency	
1278insTATC	~82%	~99%
IVS12^{+1}	~15%	
G269S	~ 2%	

1278insTATC: Myerowitz & Costigan, *JBC* 263:18587, 1988
IVS12^{+1}: Myerowitz, *PNAS* 85:3955, 1988
G269S: Paw et al., *PNAS* 86:2413, 1989

CARRIER SCREENING FOR TAY - SACHS DISEASE - 1971

Kaback et al, *JAMA* 270: 2307-2315, 1993

- Screening Program for Tay-Sachs Disease Started in 1971 by Dr. Michael Kaback at Johns Hopkins following Identification of the Enzymatic Defect
- Education of At-Risk Population and Religious Leaders Led to Wide Acceptance
- Testing Originally Done by Enzyme Assay
- Now Performed Primarily by Mutation-Specific DNA Analyses (3 Major Mutations)
- Prototype for the Prenatal Carrier Screening of Recessive Diseases

TAY-SACHS DISEASE CARRIER SCREENING*

1971 - 2006

Country	Number Tested	Carriers Identified	At-Risk Couples
United States	1,250,291	45,170	863
Israel	557,289	12,604	403
Canada	83,451	3,954	69
South Africa	18,234	1,738	55
Europe	23,789	1,548	45
Australia	8,243	312	6
Other	1,766	103	20
Total	**1,943,063**	**65,429**	**1,461**

* Data from the International TSD Data Collection Network, 2007

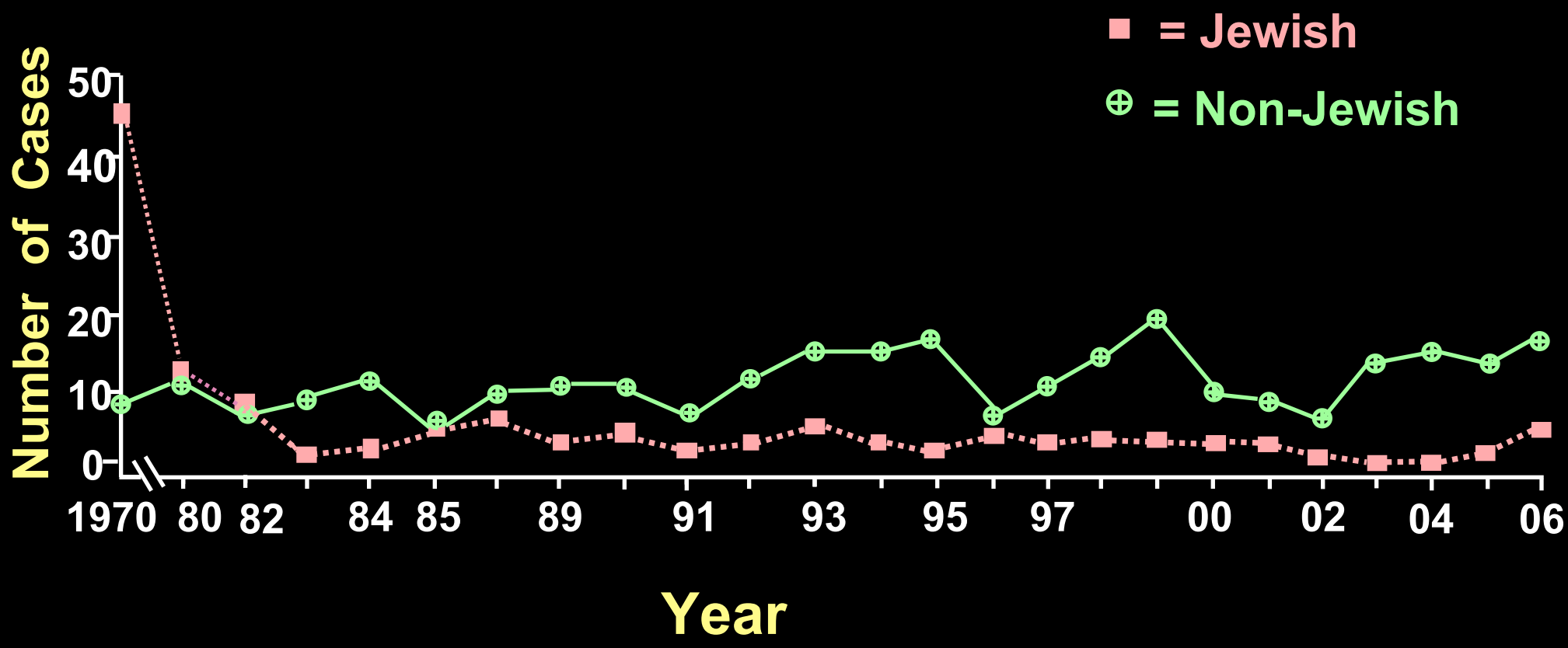
PRENATAL DIAGNOSIS OF TAY-SACHS DISEASE*

1969 - 2006

	Couples Identified At-Risk		
	By Prior Offspring	By Carrier Screening	**Total**
Pregnancies Monitored	1,675	2,309	**3,984**
Affected Fetuses	405	369	**774**
Unaffected Offspring Born	1,270	1,940	**3,220**

* Data from the International TSD Data Collection Network, 2007

NEW CASES OF TAY-SACHS DISEASE IN NORTH AMERICA*



* Data from the International TSD Data Collection Network, 2007

JAMA
The Journal of the American Medical Association
278 : 1268 - 1272, 1997
October 15, 1997

Prenatal Genetic Carrier Testing Using Triple Disease Screening

Christine M. Eng, MD; Clyde Schechter, MD; Jane Robinowitz, MS; George Fulop, MD; Tania Burget, MD; Brynn Levy, MS; Randi Zinberg, MS; Robert J. Desnick, PhD, MD

ACCEPTANCE OF PRENATAL CARRIER SCREENING*

Eng et al., *JAMA* 278:1268, 1997

Disease	Screening Method	Mutations	Detect-ability	Acceptance
Tay-Sachs	Enzyme			100%
	DNA	7	99%	
Cystic Fibrosis	DNA	70	94%	97%
Gaucher	Enzyme			95%
	DNA	8	96%	

*Based on ~5,000 Ashkenazi Jewish Individuals

PRENATAL CARRIER SCREENING IN THE ASHKENAZI JEWISH POPULATION

Disease	Frequency		No. of Mutations	Percent Detection
	Affected	Carrier		
Tay-Sachs	1 : 2500	1 : 25	7	99
Gaucher Type 1	1 : 900	1 : 15	8	96
Cystic Fibrosis	1 : 2500	1 : 25	70	97
Familial Dysautonomia	1 : 5200	1 : 36	2	>99
Canavan	1 : 6,400	1 : 60	4	97
Glycogen Storage 1a	1 : 23,000	1 : 75	2	>95
Niemann-Pick A & B	1 : 25,600	1 : 80	4	99
Maple Syrup Urine	1 : 25,600	1 : 80	3	95
Fanconi Anemia C	1 : 32,000	1 : 89	2	>99
Familial Hyperinsulinemia	1: 32,400	1 : 90	2	90
Usher III	1: 36,000	1 : 95	1	95
LAD (E3)	1 : 40,000	1 : 100	2	95
Bloom Syndrome	1 : 46,000	1 : 107	1	>99
Mucolipidosis IV	1 : 48.400	1 : 110	2	95
Nemaline Myopathy	1 : 57,600	1 : 120	1	95
Totals:		**~1 : 4**	**111**	**90-99**

ISSUES

- TSD Detectability: DNA vs Enzyme Testing
- Gaucher Disease: Clinical Variability
  Asymptomatic/Mild Disease?
- Increased Intermarriage: Residual Risk
- Prenatal Screening Not Acceptable for Orthodox and Chassidic Jews

ISSUES

- **TSD Detectability: DNA vs Enzyme Testing**
  - Enzyme Assay Detects All Carriers:
    - However, ~ 3% Inconclusive Results
  - DNA Assays Detect Specific Mutations:
    - Ashkenazi Jewish Detectability with 3 Mutations: 99%

Bach et al., Tay-Sachs Screening in the Jewish Ashkenazi Population: DNA Testing Is the Preferred Procedure. *Am J Med Genet* 99:70, 2001

ISSUES

- TSD Detectability: DNA vs Enzyme Testing
- **Gaucher Disease: Clinical Variability**
  Asymptomatic/Mild Disease?

CONTROVERSIAL ARTICLE & EDITORIAL

Article: Carrier Screening for Gaucher Disease: Lessons for Low-Penetrance, Treatable Diseases

Zuckerman et al., *JAMA* 298:1281-1290, 2007

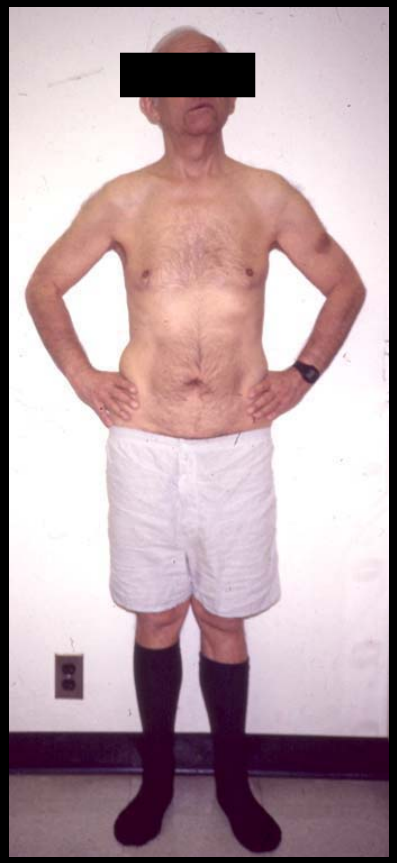
Editorial: Carrier Screening for Gaucher Disease: More Harm than Good?

Beutler, *JAMA* 298,1329-1331, 2007

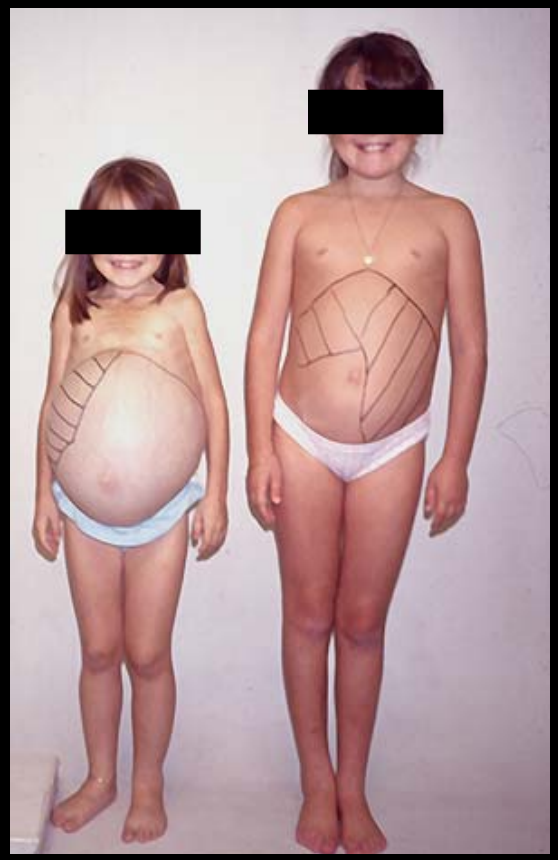
- Suggests that 2/3 of N370S/N370S Homozygotes Are Asymptomatic Throughout Life ("Low Penetrant")
- Therefore, Screening Carriers for Low Penetrant Diseases May Cause Harm

TYPE I GAUCHER DISEASE
N370S/N370S HOMOZYGOTES

Same Genotype - Different Phenotypes



Mild



Severe

AFFECTED GAUCHER PATIENTS DETECTED BY MOUNT SINAI PRENATAL SCREENING PROGRAM

	Number	%	Frequency	
			Observed	Expected
Screened	8069	100	-	-
Carriers	524	6.5	1 in 15.4	-
Affected	9	0.1	**1 in 897**	**1 in 949**

8069 Ashkenazi Jewish Individuals Screened for Gaucher Disease
As Part of the Prenatal Carrier Screening Program

GAUCHER PATIENTS DIAGNOSED BY PRENATAL SCREENING PROGRAMS

- 35 Gaucher Patients Diagnosed by Prenatal Screening Programs (28 Female & 7 Males; Ages: 17-40 Yr)
  - 91% (32/35) Had the Mild to Severe N370S/N370S or N370S/R496H Genotypes
- 2/3 of Patients Reported No Clinical Symptoms

- 54% Had Mild to Moderate Anemia or Thrombocytopenia
- 96% Had Mild to Moderate Splenomegaly
- 57% Had Mild to Moderate Hepatomegaly
- 55% Had Osteopenia
- 96% Had Bone Involvement (e.g., Infiltration, Erlenmeyer Flask Deformity, Infarcts, Osteopenia)

ISSUES

- TSD Detectability: DNA vs Enzyme Testing
- Gaucher Disease: Clinical Variability
  Asymptomatic/Mild Disease?
- **Increased Intermarriage: Residual Risk**

INTERMARRIAGE OF JEWS IN THE UNITED STATES*

Marriage Year	% Intermarriage
Up to 1940	2-3
WWII to 1960	7
1961-1965	17
1966-1972	>30
1985-1990	52

*American Jewish Year Book, 2007

INCREASED INTERMARRIAGE

- Jewish Spouse Carrier Risk: 1:4 for 16 Recessive Diseases
- Non-Jewish Spouse Has Much Lower Carrier Risk
- Jewish Carriers and their Non-Jewish Spouses Experience Increased Anxiety
- Residual Risk Counseling and/or Gene Sequencing Should Be Offered

ISSUES

- TSD Detectability: DNA vs Enzyme Testing
- Gaucher Disease: Clinical Variability
  Asymptomatic/Mild Disease?
- Increased Intermarriage: Residual Risk
- **Prenatal Screening Not Acceptable for Orthodox and Chassidic Jews**

UNIQUE CONSIDERATIONS FOR CARRIER SCREENING IN THE RELIGIOUS COMMUNITY

- Prenatal Diagnosis Is Not Feasible
  - Abortion Not Permitted
- Artificial Insemination by Donor Is Not an Option
- Birth Control Is Not Acceptable

UNIQUE CONSIDERATIONS FOR CARRIER SCREENING IN THE RELIGIOUS COMMUNITY

- **Marriages Arranged: "Quality of the Match"**
  - Girls Marry at ~18 Yr; Boys in Early 20s
  - Health of Spouse and Their Family Important
  - Fear of Stigmatization Due to Diseases in Family
- **Large Families are Encouraged:**
  - Many Families have 5 to 10 Children

"CHEVRA DOR YESHORIM"

GENETIC SERVICES IN THE RELIGIOUS COMMUNITY

- **"Compatibility Testing"**
  - **– Genetic Screening Prior to "Matches"**
- Genetic Counseling: Consanguineous Matches
- Diagnosis and Management of Genetic Diseases

CHEVRA DOR YESHORIM

COMMITTEE TO PREVENT JEWISH GENETIC DISEASES

"COMPATIBILITY TESTING"

1983-2006

Over 200,000 Young Singles Screened

Proposed Matches of Carriers Prevented: > 825

SAUDI ARABIA