

Genetic Disorders and the Jewish Population

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From Generation to Generation: The Genetics of Jewish Populations

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Outline

- Genetic diseases found in Ashkenazi Jews. Why?
- Some background on genetics of Ashkenazim
- History of recessive lysosomal storage diseases
- Founder effects versus selection – the raging debate
- Are all Jewish genetic diseases recessive? The case of primary torsion dystonia
- What is current state of knowledge on AJ diseases
- Conclusions

Jewish History and Genetics

- The 3,000+ year history of the Jewish people has been one of expansions and contractions, separations, migrations and coalescence. This unique history has left its mark through the genetic profiles of the various extant Jewish communities of today

Classification of Jews

- For the study of genetics, Jews can be categorized into several groups based on geography, history and culture. These groups are not entirely non-overlapping, however, due to historical migrations even during times of separations.

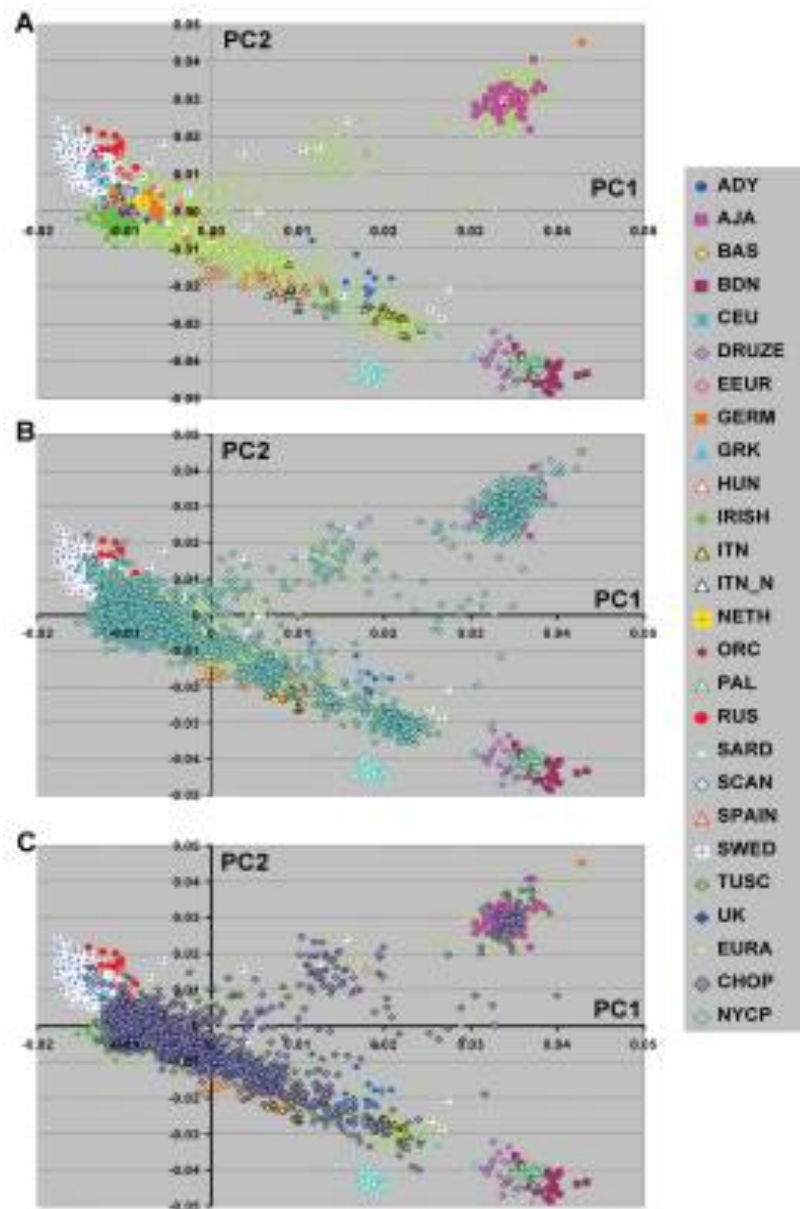
Classification of Jews

- Ashkenazi
 - Central/Eastern European. Origins in Central Europe (France, Germany) in 10th century
- Sephardic
 - Origins in Spain and Portugal (probably from first century or earlier); migrated to Eastern Mediterranean (Turkey – 90,000) and parts of Europe (Holland – 25,000; France – 10,000; Italy – 10,000), North Africa (Morocco – 20,000) and America (5,000) after Spanish and Portuguese Inquisitions (1492 and 1497)
- Oriental
 - Middle East, North Africa, India (ancient times)

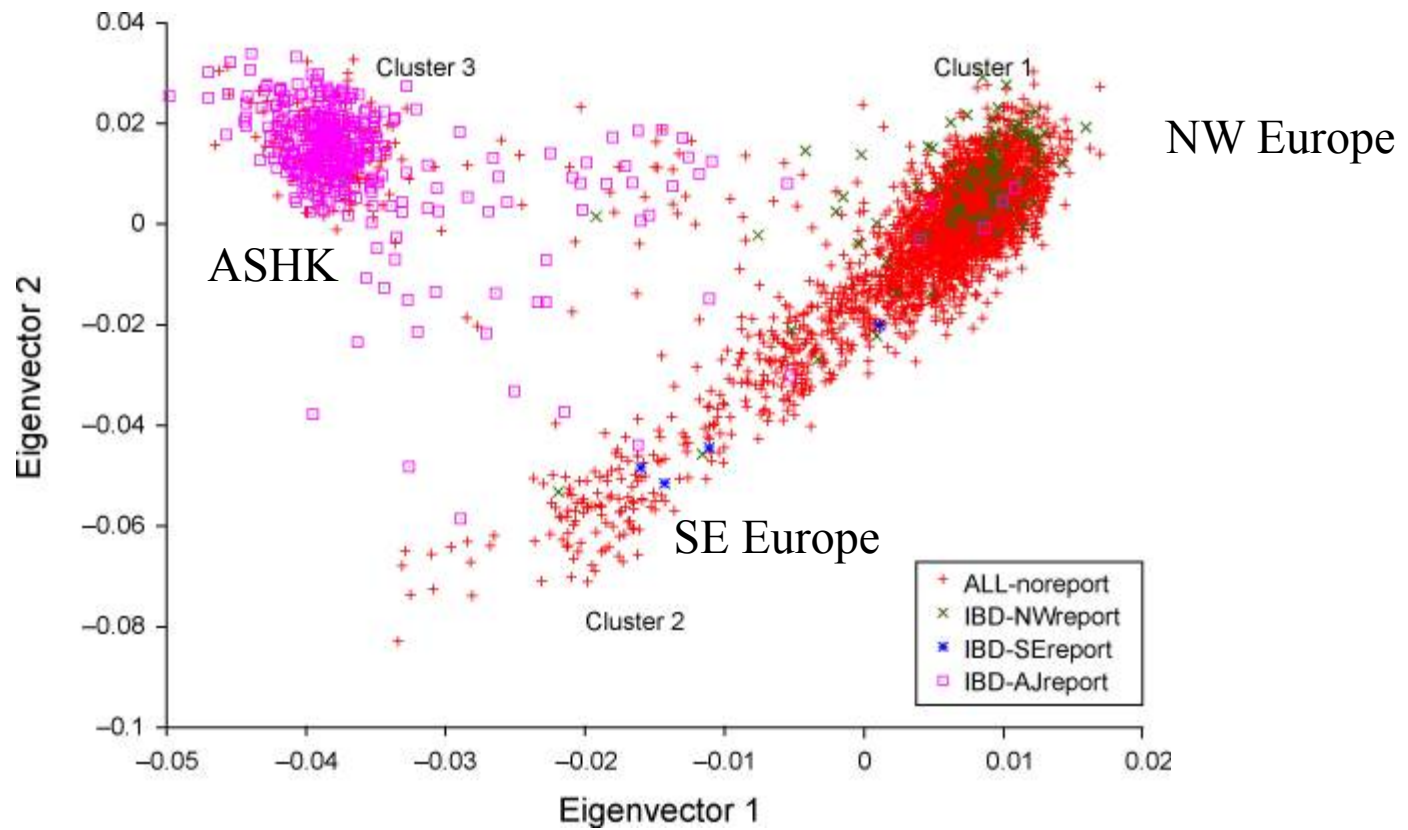
Background on Ashkenazi Genetics

- A number of population genetic studies have looked at the genetic constitution of Jews, in particular with respect to other European and Middle Eastern populations.
- The results of these studies have been highly consistent in showing that Ashkenazim constitute a distinct genetic subgroup.

Tian et al, Molecular Medicine (2009)



Price et al, PLoS Genetics (2008)



Ashkenazi Genetics - Summary

- Among European/Middle Eastern populations, Ashkenazim are genetically most similar to Eastern Mediterranean populations, such as Greeks and Southern Italians
- However, they are more distant from those groups than those groups are to each other
- This pattern is similar to Sephardic Jews, except Sephardic Jews are closer overall to Mediterranean non-Jews

Genetic Diseases in Jews

- The pattern of genetic diseases in the Jewish population reflects both their common ancestry and independent developments
- Some mutations are found in several Jewish groups: The breast cancer mutation BRCA1 185delAG (Ashkenazi Jews, Iraqi Jews, Iranian Jews, Moroccan Jews, Spanish Jews); the colon cancer mutation I1307K (Ashkenazi Jews, Iraqi Jews); Factor XI mutation II (Ashkenazi Jews, Iraqi Jews)

Diseases in Ashkenazim

- The Ashkenazi Jewish (AJ) population is known to have a number of genetic diseases at increased frequency
- Prominent among these are four lysosomal storage diseases (LSDs): Tay-Sachs Disease (TSD), Gaucher Disease (GD), Niemann-Pick Disease (NPD) and Mucopolysaccharidosis Type IV (MPS IV)

Lysosomal Storage Diseases

- Recessive inheritance
- Genetic defects resulting in enzyme deficiency
- Absence of enzyme prevents the lysosome in the cells of the body from performing its natural recycling function, so various materials are inappropriately stored in the cell

Lysosomal Storage Disease

- This leads to a variety of progressive physical and/or mental deterioration over time.
- Some patients survive into adulthood, but others have more severe symptoms and die in their teens or earlier
- Currently 46 different LSDs, four of which occur within Ashkenazi Jews

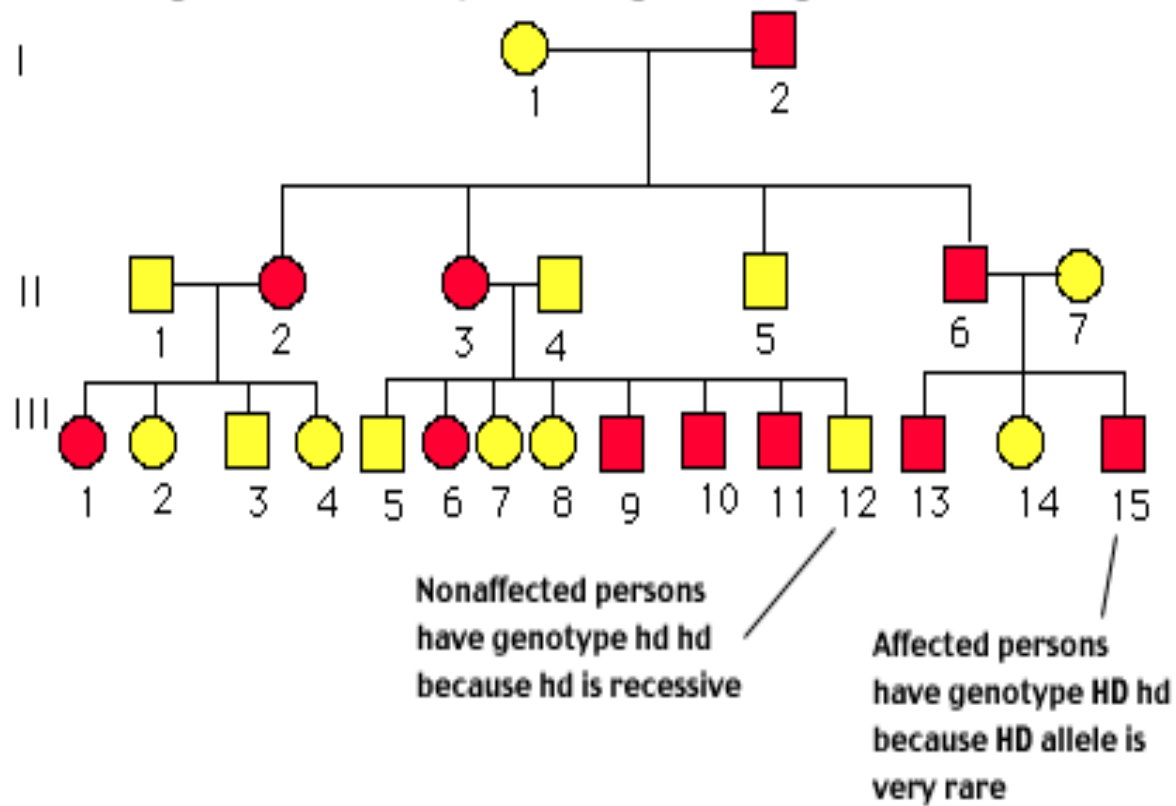
Diseases in Ashkenazim

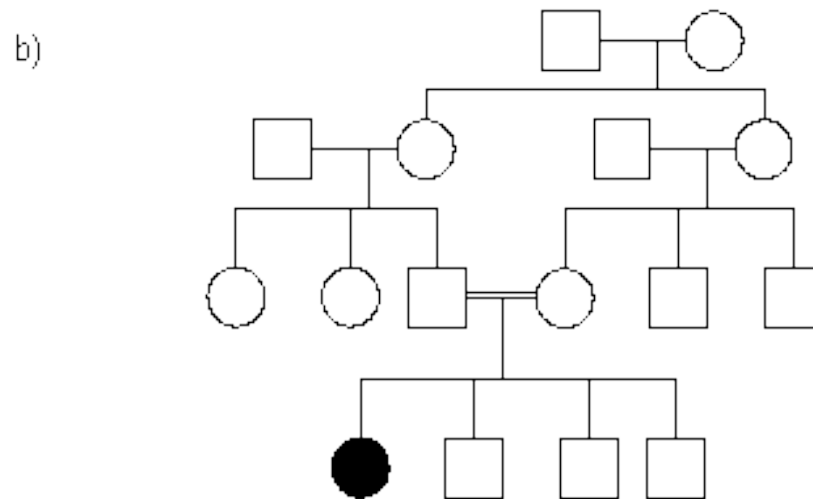
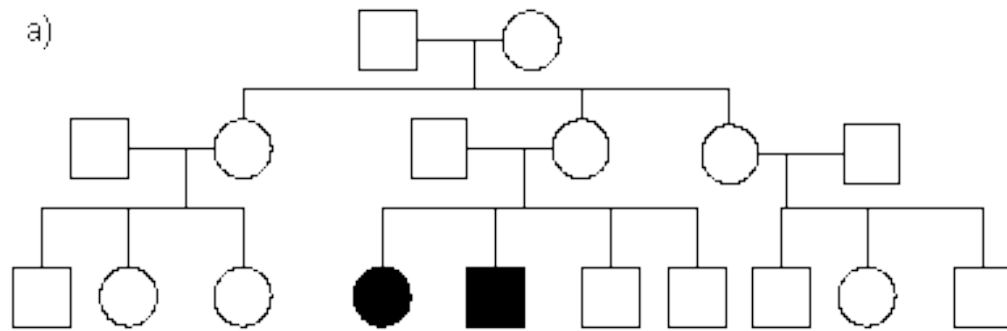
- Historically there has been extensive debate over the reason for the increased frequency of four LSDs in the AJ population, between genetic drift (founder effects) versus natural selection (heterozygote advantage)

Dominant vs Recessive Inheritance

- Dominant inheritance refers to the case where carrying a single copy of a mutation will lead to disease. Dominant diseases are transmitted through every generation in a pedigree, from parent to child.
- Recessive inheritance requires two copies of a disease mutation, one from each parent. Hence, affected sibships are observed but rarely across generations. Parents are unaffected carriers.

Pedigree of a family showing Huntington disease

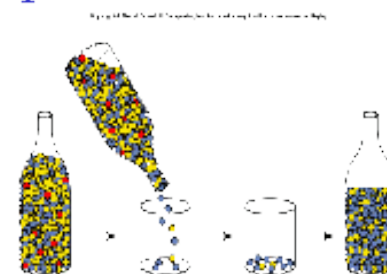




Pedigrees of recessive inheritance

Genetic Drift

- **Small populations:** allele frequency may change by chance
- **Founder effect:** few individuals migrate and form new population; may not carry all alleles; previously rare alleles can become dominant
- **Bottleneck effect:** catastrophic events (floods, diseases) leave few survivors that may not carry all alleles present in original population



Genetic Drift

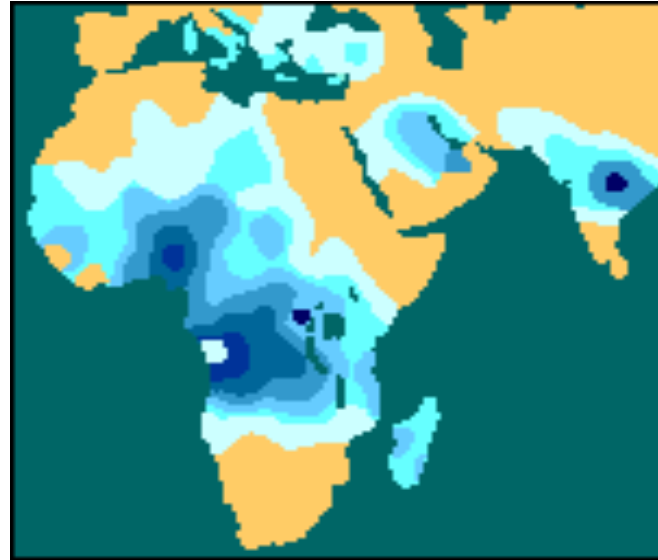
- Change in allele frequencies by random chance alone, due to small population size
- Can occur during the founding of a population (founder effect) or the dramatic reduction in population size before recovery (bottleneck effect)

Heterozygote Advantage (selection)

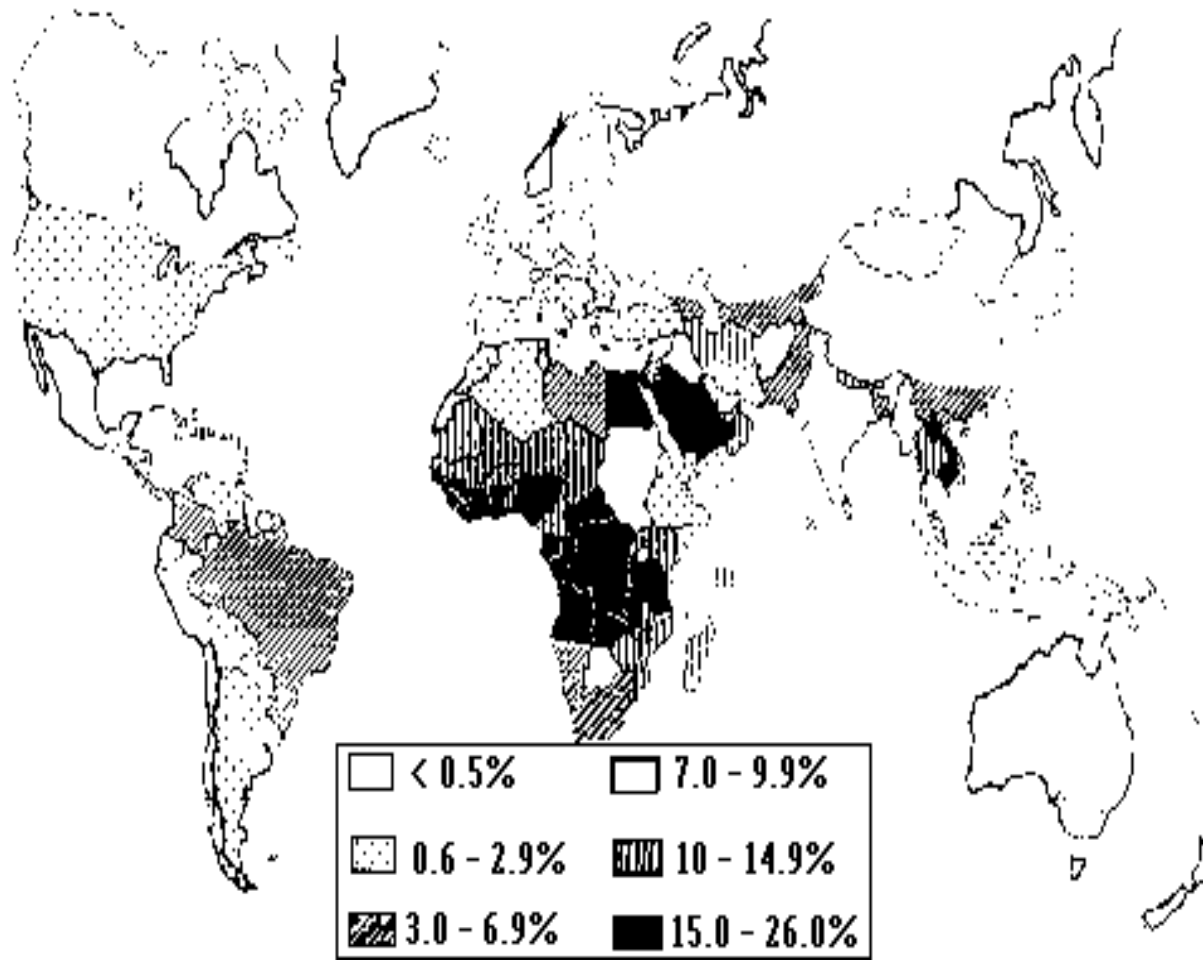
- For a recessive disease, even though it may be serious and even fatal, those who carry a single copy of the mutant allele (heterozygote) may have a survival advantage over those who have a normal genotype
- If so, the mutant frequency will increase because of the heterozygote advantage, even at the expense of losing the affected homozygotes

Classic Example of Heterozygote Advantage

- Hemoglobinopathies (Sickle Cell Disease; beta thalassemia)
- Carriers of lethal mutations (when homozygous) have some protection against malaria
- Other, less serious mutations also observed (e.g. G6PD deficiency)



Distribution of sickle cell (top) and malaria (bottom)



Distribution of G6PD Deficiency

Ecological Correlations

- Geographic correlations between genetic variants and disease represent ecologic correlations, but do not imply causality.
- However, in this case, multiple different genetic variants, in different populations, correlated with malaria prevalence, increasing index of suspicion
- Generally, direct evidence of genetic protection in heterozygotes is necessary to prove selection. Such studies have been done in Sickle Cell Disease and malaria in Africa

Back to Ashkenazi Diseases

- While the lysosomal storage diseases (TSD, GD, NPD, MLIV) have featured most prominently in discussion of Ashkenazi genetic diseases, the Ashkenazi population is also affected by a substantial number of genetic diseases at increased frequency that do not involve lysosomes.

Are founder mutations always recessive?

- The case of Primary Torsion Dystonia
 - Elevated frequency in Ashkenazim
 - Originally thought to be recessive because of likely founder effect and/or selection
 - However, further careful analysis of family members revealed an autosomal dominant pattern of inheritance with reduced penetrance
 - Further gene mapping revealed a large extended haplotype around the mutation, indicating a recent founder event

Am J Hum Genet. 1990 March; 46(3): 533–538.

Segregation analysis of idiopathic torsion dystonia in
Ashkenazi Jews suggests autosomal dominant
inheritance.

N J Risch, S B Bressman, D deLeon, M F Brin, R E Burke, P E
Greene, H Shale, E B Claus, L A Cupples, and S Fahn

Am J Hum Genet. 1992 March; 50(3): 619–628.

Strong allelic association between the torsion
dystonia gene (DYT1) and loci on chromosome 9q34
in Ashkenazi Jews

Laurie J. Ozelius, Patricia L. Kramer, Deborah de Leon, Neil
Risch, Susan B. Bressman, Deborah E. Schuback, Mitchell F.
Brin, David J. Kwiatkowski, Robert E. Burke, James F.
Gusella, Stanley Fahn, and Xandra O. Breakefield

Other Genetic Diseases found in Ashkenazim

- Bloom Syndrome (BLM), Breast Cancer (BRCA1, BRCA2), Colon Cancer (APC), Canavan Disease (CAN), Deafness (CX26), Cystinuria (CYS), Dysautonomia (DYS), Factor XI Deficiency (FX11), Familial Hyperinsulinism (FI), Familial Hypercholesterolemia (FH), Fanconi Anemia Type C (FACC), Glycogenesis type 7 (GLY7), Tarui Disease (PFKD), Torsion Dystonia (DYT1), Galactosidase Deficiency (GALT), Parkinson Disease (LRRK2)

Genetic Diseases in Jews

- While most genetic diseases found in the Ashkenazi population are recessive, some are dominant:
 - Primary Torsion Dystonia
 - BRCA1 and BRCA2
 - Familial Hypercholesterolemia

Ashkenazi Diseases

- To address the question of natural selection (heterozygote advantage) for the LSDs, it is relevant to compare the LSDs versus the non-LSDs in a variety of ways:

Genetic Diseases in Ashkenazim

- 1. The number of different mutations found in each gene underlying the disease
- 2. The frequency distribution of the mutations for LSDs versus non-LSDs
- 3. The ages (coalescence dates) for LSD versus non-LSD mutations
- 4. The European ancestral geographic distribution of LSD versus non-LSD mutations

Genetic Diseases in Ashkenazim

- Differences between the LSDs and non-LSDs for any of the above characteristics would be suggestive of specific selection effects operating on LSDs; on the other hand, similar patterns would argue in favor of founder effect and genetic drift as the primary explanation.

Ashkenazi Diseases

- Furthermore, disparities in age and/or geographic localization for different mutations within the LSD group would also argue against selection, since the selection would be most likely to occur specifically in time and place

Ordered Frequencies for LSD Mutations in Ashkenazim

<u>Disease</u>	<u>Mutation</u>	<u>Frequency</u>
GD	1226	.032
TSD	1277	.013
NPD	1302	.005
MLIV	IVS3	.004
TSD	1421	.003
GD	84GG	.002

Ordered mutation frequencies for non-LSDs in Ashkenazim

<u>Disease</u>	<u>Mutation</u>	<u>Frequency</u>	<u>Disease</u>	<u>Mutation</u>	<u>Frequency</u>
APC	I1307K	.035	FACC	IVS4	.006
FXI	III	.025	BRCA1	185delAG	.006
FXI	II	.022	BRCA2	6174delT	.006
CX26	167delT	.020	FI	3992	.006
DYS	IVS20	.016	BLM	2281	.005
PNT	583delC	.014	CF	F508	.005
CAN	854	.012	CX26	35delG	.004
CYS	808C->T	.008	USH3A	N48K	.004
CF	1282	.008	GALT	5.5DEL	.004
GSD1a	R83C	.007	FH	G197del	.003
PD	G2019S	.007	CAN	693	.002

Mutation Frequencies

- Thus, there is no difference in the frequency distribution for mutations that cause the LSDs and the other non-LSDs.

Dating Mutations

- It is possible to determine approximately the date of origin of mutations in a population
- This is done by looking at (neutral) genetic markers near the disease mutation
- In each generation, there is a certain (low) probability, through the process of genetic recombination, for the nearby marker(s) to recombine with the disease mutation

Dating Mutations

- Thus, by examining a group of disease mutation bearing chromosomes for nearby markers with known recombination distance, and seeing how many still have the original marker alleles you can calculate approximately how many generations have passed (although confidence intervals may be large).

Estimated times of origin of various mutations

<u>Lysosomal Storage Diseases</u>			<u>Other Diseases</u>		
<u>Disease</u>	<u>Mutation</u>	<u>Gens</u>	<u>Disease</u>	<u>Mutation</u>	<u>Gens</u>
GD	1226	48	FXI	III	31
MLIV	IVS3	57	FXI	II	120
GD	84GG	55	DYS	IVS20	52
			BLM	2281	50
			BRCA1	185delAG	46
			BRCA2	6174delT	29
			FH	G197del	12
			PTD	delGAG	12

Times of Origin

- Among the mutations found in Ashkenazim, two are known to occur at very high frequency in Jews from Lithuania – the torsion dystonia mutation delGAG and the familial hypercholesterolemia mutation G197. Both mutations date to about 12 generations, or about 400-500 years ago, corresponding to the founding of the Lithuanian Jewish population

Times of Origin

- Most other mutations date to 45-55 generations ago, corresponding approximately to the time of founding of the Ashkenazi population in Europe 1100 years ago.
- Overall, there is no difference in times of origin of the LSD and non-LSD mutations

Geographic Distributions of Mutations - Dor Yeshorim Screening Program

- Brooklyn, New York
- Service to the Orthodox Jewish Community around the world
- Genetic testing of high-school senior girls and boys, prior to marriage
- Mutation analysis for 7 recessive genetic diseases

Dor Yeshorim Screening Program – Diseases Tested

Lysosomal Storage Diseases

Tay-Sachs

Gaucher

Niemann-Pick

Non-lysosomal Storage Diseases

Canavan

Bloom Syndrome

Fanconi Anemia C

Cystic Fibrosis

Dor Yeshorim Screening Program

- For each testee, geographic origin of four grandparents obtained, if known
- Allele frequencies were estimated for each country of origin (with sufficient numbers), as well as for larger geographic areas. The following regions were defined:

Geographic Categories:

- Central Europe
 - (Austria, Hungary, Czechoslovakia, Romania)
- Eastern Europe
 - (Poland, Russia, Lithuania)
- Mediterranean
 - (North Africa, Greece, Italy, Turkey)
- Mideast and Southern former USSR

Mutation Frequencies for LSDs

<u>Region</u>	<u>Mutation</u>						
	<u>Gaucher Disease</u>			<u>NPD</u>	<u>Tay-Sachs Disease</u>		
	<u>1226</u>	<u>1604</u>	<u>84GG</u>	<u>1302</u>	<u>1277</u>	<u>1421</u>	<u>G269</u>
C. Europe	.0382	.0023	.0050	.0036	.0218	0	.0003
E. Europe	.0303	.0032	.0006	.0010	.0175	.0041	.0010
Mediterr.	.0028	.0006	0	0	0	0	0
Mid East	0	0	0	0	0	.0005	0

Frequency of TSD 1421 mutation in Eastern Europe

<u>Region</u>	<u>Frequency</u>
Lithuania	.0113
Russia	.0067
Poland	.0022

Conclusions

- Ashkenazi Jews form a genetically distinct population
- This is likely due to genetic drift and endogamy over the past 1000 years
- Genetic disease founder effects are a consequence of small historic population size and endogamy

Conclusions

- A wide variety of genetic diseases occur in the Ashkenazi population; many are recessive, but some are dominant
- The clinical range is broad, strongly suggesting founder effects rather than heterozygote advantage

Conclusions

- Regarding the LSDs, none of the observed distributions differed between LSDs and non-LSDs: number of mutations, frequency distribution of mutations, coalescence dates of mutations, or geographic ancestry of mutations.

Conclusions

- We observed a higher frequency of TSD 1277 (and the two GD mutations 1226, 84GG) in Central Europe than in Eastern Europe
- The (likely) recent Lithuanian distribution of TSD 1421 in contrast to the more central (and likely older) distribution of TSD 1277, also cast doubt on the theory of heterozygote advantage for the LSD mutations, and favors simple founder effect (genetic drift) as the primary explanation

Conclusions

- Three bottlenecks in Jewish history appear to be important regarding disease alleles in the Ashkenazim:
 - The founding of Jews >2000 years ago (e.g. Factor XI II mutation, also found in Iraqi Jews at a similar frequency)
 - The founding of the Ashkenazim ~ 1100 years ago (e.g. GD 84GG, MLIV IVS3 and DYS IVS20)
 - The founding of Lithuanian Jews ~ 500 years ago (e.g. PTD delGAG, FH G197del and TSD 1421)

The Future

- The future of Jewish genetic diseases will be influenced by Jewish demography
- Screening is now available for many or most of these inherited diseases
- Increasing intermarriage rates in the US among the non-Orthodox will lead to lower frequencies in that group and greater genetic heterogeneity
- In Israel, mixing of Jews of various geographic origins will have a similar effect