

Rabbi Joseph Kelman ob''m April 1,1927-June 27, 2009 (ה' תמוז, תשס"ט)
Rabbanit Ruth Kelman ob''m August 20, 1933 - June 12, 1999 (כח' סיון, תשנ"ט)

The Genetic History and Future of the Jewish People



The Genetic History and Future of the Jewish People

Is there a Jewish People?



Can we learn about human history from DNA?

What can we learn about the past history of Jews from the DNA of contemporary Jews?

Are there societal, political, legal, health, halachic implications that might impact on the future?

Back to the future!

Case 1

30 year old Israeli woman is to marry an Israeli Jewish man in Israel. The woman immigrated at the age 12 from the Ukraine under the "Law of Return". There is documentation for Jewish identity of her paternal grandfather, but no comparable record as her maternal side.

The Rabbinical Courts in Israel refuse to grant a marriage permit. She carries out private DNA testing which shows that her mitochondrial (maternally transmitted) DNA is of the K1a1b1a sublineage shared with 1.5 millions of established Jews, while was found only in one non-Jew(?) subject from west Ukraine in a 13500 non-Jewish European sample set.

Does the woman need conversion?

Case 2

26 year old religiously observant Kohen (AA) was introduced to the 22 old year daughter (BB) of a Kohen (CC), who had married a divorcee, rendering the daughter halachically a "Chalala" and hence forbidden to marry BB.

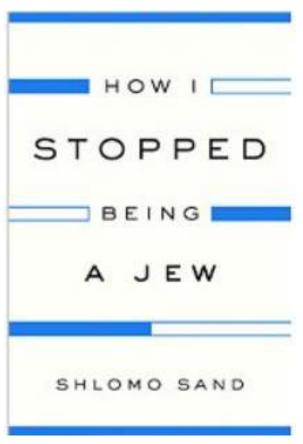
AA asked the following question: if Y chromosome DNA marker testing shows that AA and CC come from paternal genealogic lineages which diverged long before the time of Biblical Aaron HaKohen, then one or both of us is not from the "seed of Aaron".

- Is the scientific rationale valid?
- Are there halachic implications?

Secondary question: How many Kohanim are needed for a valid Pidyon HaBen

The Genomic History of the Jewish People

Is there a Jewish People?



Shlomo Sand



Hillel Halkin
"Indecent Proposal"
Book Review
January 9, 2010



The Genetic History of the Jewish People

Is there a Jewish People?



Martin Gilbert z"l

Tudor Parfitt



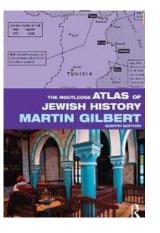
Sergio Della Pergola

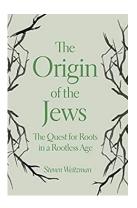


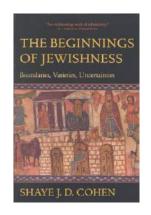
Steven Weitzman

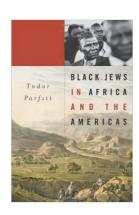


Shaye Cohen









many other.....



Can we learn about human history from DNA?



- DNA marker evidence indicates that all humans are part of one extended family
- DNA marker evidence indicates that Jews scattered across most Diaspora communities are members of a branch of this extended family originating in the Near East ~ 3,000 years ago

But more complex than that!



the power of DNA:

Biological Sciences

Medical Genetics

Genetic Archaeology:

Genetic Anthropology: Human Origins

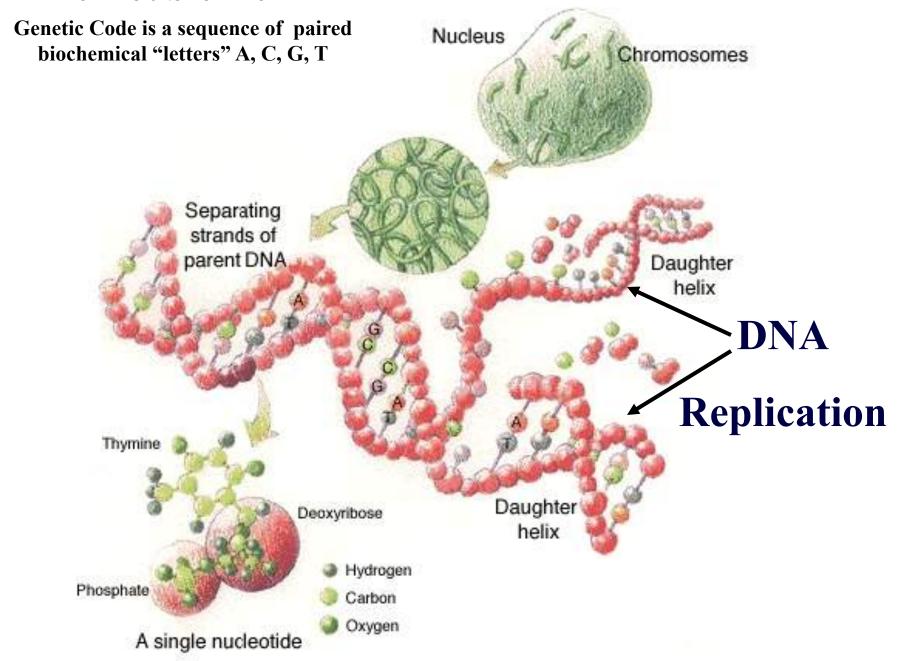
Population Genetics: Demographics, Communities

Genetic Genealogy: Families, Lost Relatedness, Forensics





The Double Helix



DNA Replication

Precise → no errors

boring world full of identical copies of same sequence

Errors — richness of living diversity

price: illness

ורפוא ירפא...



...and you shall surely heal Exodus 21, 18

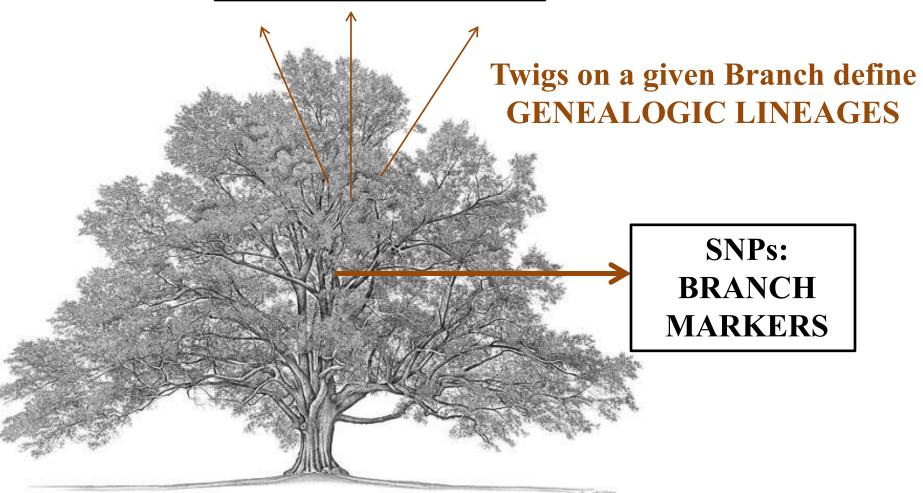


Mutations and Markers

Most (~95%) errors in DNA replication are "silent": Do not cause differences in appearance or behaviour or disease, but they can be detected as markers by DNA analysis

These markers are used in Population Genetics to trace ancestries and to map real disease causing mutations

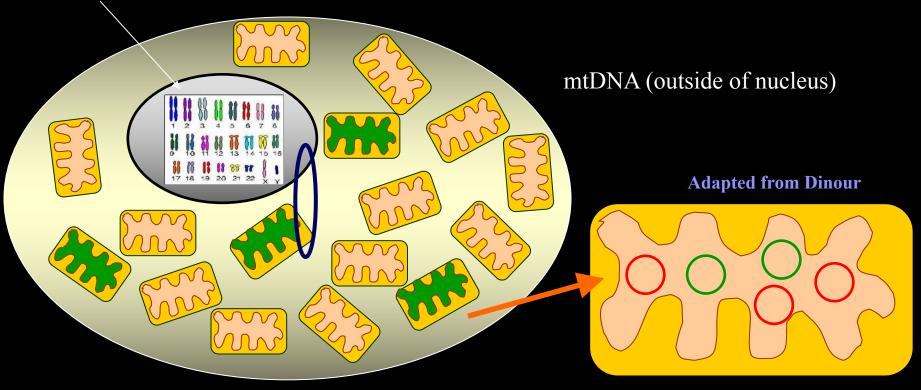
STRs: TWIG MARKERS



"For man is but the tree of the earth"

Location of Genomic DNA Markers

Chromosomes in nucleated cells





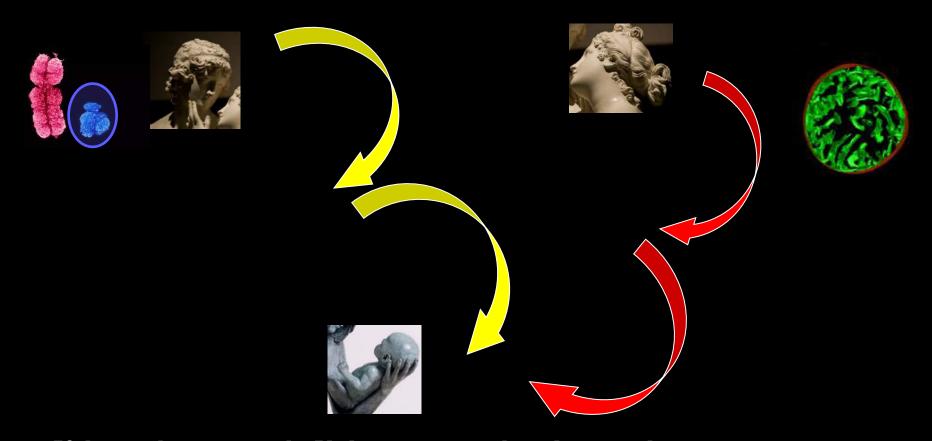
Y Chromosome markers only in males



Mitochondrial markers only transmitted by females

Reconstructing Ancestry

Individuals who share the same set of markers for a given DNA region share a common ancestry at that genomic region

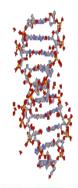


If the markers are on the Y-chromosome – shared paternal ancestry

If the markers are on mitochondrial DNA – shared maternal ancestry



It Began with the Cohanim





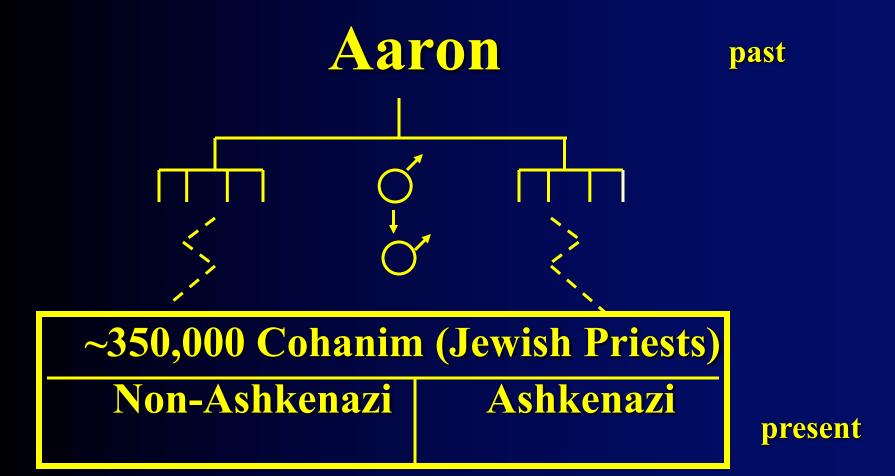


"And take unto thee, Aaron thy brother, and his sons with him, from among the children of Israel, that he may minister unto me in the priest's office..." Exodus 28,2

http://www.jewsnews.co.il/2014/05/19/the-fascinating-jewish-story-behind-the-star-trek-vulcan-salute/

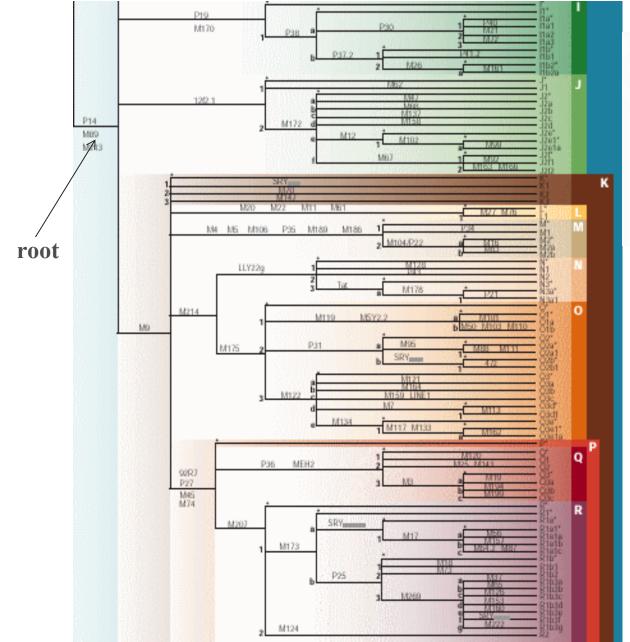


Credit: Stephen Gryfe

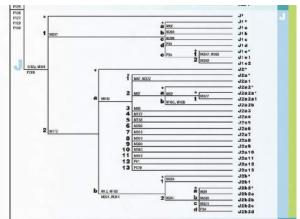


HYPOTHESIS: Y-chromosomes of historically and geographically dispersed Cohanim should be more alike than Y's of other groups and more alike than are their autosomes

(p.s. anyone can do this today and check in 100 generations)



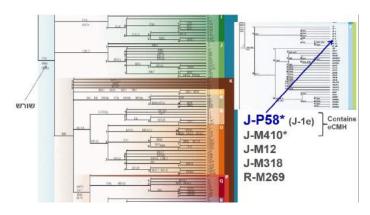
Y-Lineage Tree



Y-Chromosome
Global
Haplogroup Tree
(Branches)
Will the
Kohanim be
dispersed among
many or few
branches?







SCIENTIFIC CORRESPONDENCE

nature

trast, we found no significant difference in

the distribution of alleles for the non-Ychromosome locus polymorphism D1S191

(data not shown). These Y-chromosome

We further identified subjects as being

of Ashkenazic or Sephardic origin. This

paternal genealogy for Jewish priests.

Y chromosomes of Jewish priests

HAPLOTYPE FREQUENCY Fistandard error

between Jewish priests and their lay 7 million (data not shown). counterparts. Remarkably, the difference

(0.020)

Sig. — According to biblical accounts, the than paternal descent by which male Jews Jewish priesthood was established about are assigned to the priesthood. Identifica- haplotype differences confirm a distinct 3.300 years ago with the appointment of tion as a priest carries with it certain social the first Israelite high priest. Designation and religious obligations which have tendof Jewish males to the priesthood con- ed to preserve this identity within Jewish tinues to this day, and is determined by communities. Based on surveys of Jewish refers to the two chief, separate communistrict patrilineal descent, Accordingly, we cemetery gravestones, priests represent frequency of Y-chromosome haplotypes male world Jewish population of roughly

ties which developed within the diaspora sought and found clear differences in the approximately 5% of the estimated total during the past millennium. As shown in the table, the same haplotype distinction can be made between priests and lay We identified haplotypes of 188 unre-members within each population. This is observable in both the Ashkenazic lated Y chromosomes using the poly-result is consistent with an origin for the and Sephardic populations, despite the merase chain reaction (PCR) applied to Jewish priesthood antedating the division geographical separation of the two genomic DNA isolated from buccal of world Jewry into Ashkenazic and mucosal swab samples from Israeli, North Sephardic communities, and is of particu-The human Y chromosome has useful American and British Jews, We construct lar interest in view of the pronounced properties for studies of molecular evolu- ed haplotypes using first, the presence or genetic diversity displayed between the tion1.3. Except for the pseudo-autosomal absence of the Y Alu polymorphic (YAP) two communities1. This conclusion is furregion, it is inherited paternally and does insert, thought to represent a unique evonot recombine. It can be used to construct lutionary event dated to between 29,000 ance of the YAP. DYS19B haplotype in patrilineal genealogy cladograms comple- and 340,000 years ago¹³; and second, a both populations, suggesting that this may have been the founding modal haplotype

Sephardic Ashkenatic: Cohen Israelite n=81 0.205 (0.045) (0.061) (0.029)(0.056)somes of Jewish priests during the relatively short time since the establish-0.544 0.325 0.454 0.321 ment of the priesthood, should be useful (0.075)(0.052) (0.093) (0.060) (0.042) in defining rates and mechanisms of Y-0.042 0.359 0.162 0.300 0.227 0.272 chromosome evolution. (0.045) (0.042) (0.063)(0.049)(0.041) Karl Skorecki 0.083 0.091 0.026 Sara Selig (0.035)(0.044)(0.035)(0.056)(0.024) (0.024) Shraga Blazer 0.083 0.029 0.000

> 0.000 0.153

of the Jewish priesthood. Taken together, our findings define a set of Y chromosomes of recent common origin. Differences which have accumulated in the genomic DNA of the Y chromo-

Bruce Rappaport Faculty of Medicine and Research institute and Rambam Medical Centre Technion-Israel Institute of Technology

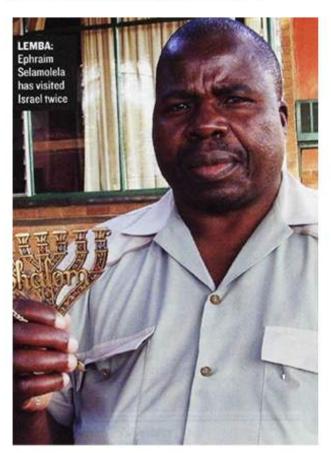
A remarkably limited number of Y-chromosome lineages shared among Kohanim from temporally and geographically dispersed Diaspora communities

- The largest such branch coalesces to a founder ~3,200 ybp with a Levant origin and is designated by a suite of markers defining the signature: "Cohen Modal Haplotype" (eCMH)
- Consistent over more than 20 years of research which gave rise to several consumer genetic genealogic companies:
 - **FamilytreeDNA**
 - **National Genographic**
 - many other

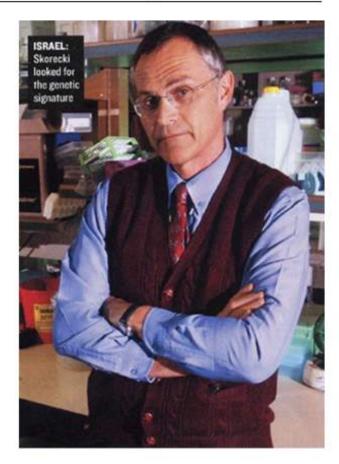


"Lost Tribes and Hidden Jews"

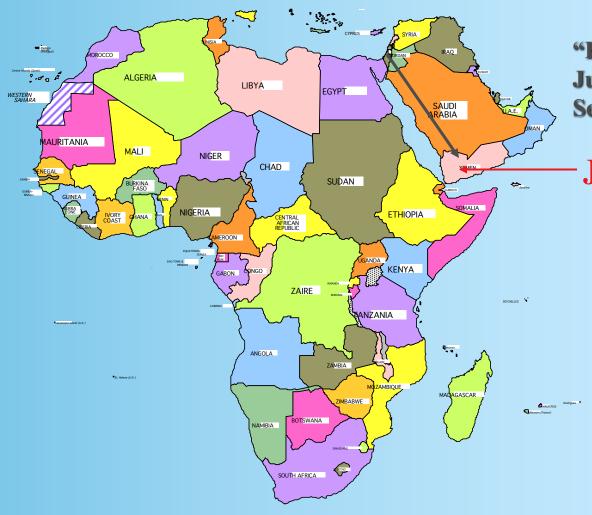




Are They Related?



Traditional History of The Lemba

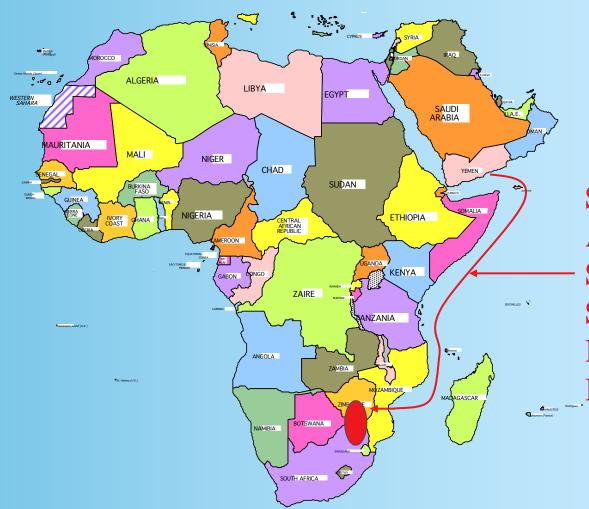


"Buba" led a group out of ancient Judea – to settle in the city of Senna in the Hadramout

Jewish Deme in Yemen

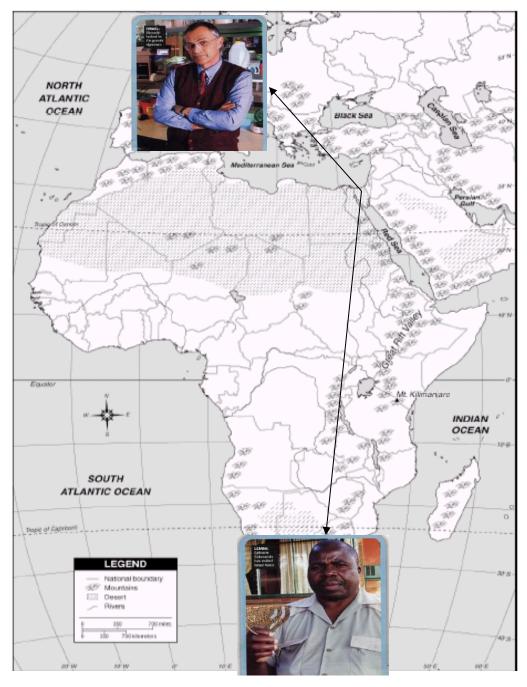
Tristan da Cusha Group (U.)

Traditional History of The Lemba

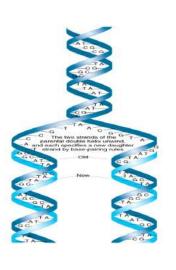


Several Centuries Ago, A Boat of Jewish Men Sailed From Yemen to Southern Africa, Went Inland and Married Local Bantu Women. Y-chromosome signatures indicate that many Lemba and many Cohanim share highly resolved Near East paternal ancestry

Could not have guessed by physical appearance nor by looking at markers outside of Y



Male genealogic relatedness does not necessarily reflect "genome wide" relatedness nor how each individual will respond to a given medication



Each Genomic Region has its own Evolutionary History

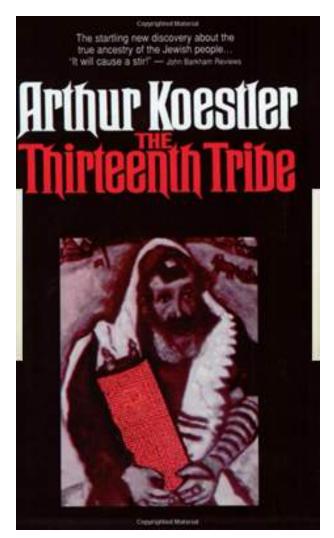


"Lost Tribes and Hidden Jews"

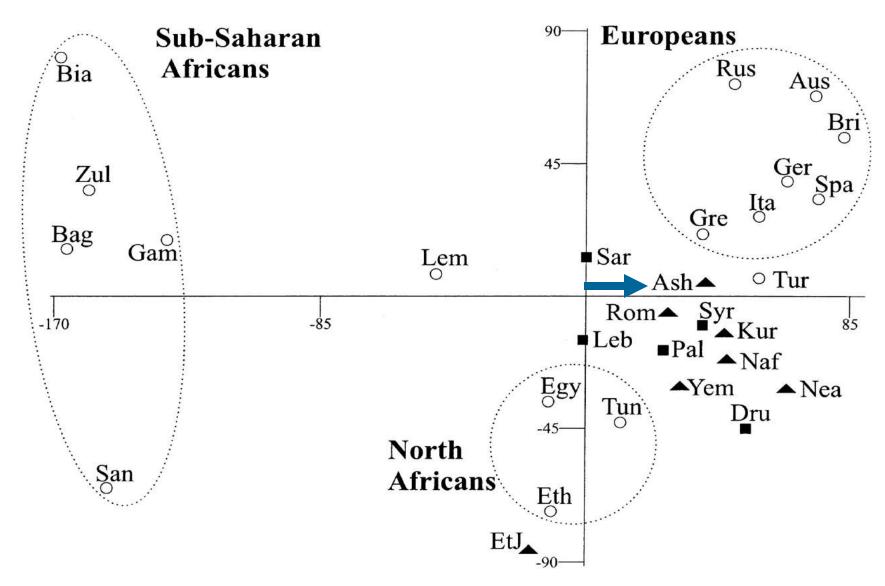
Are Ashkenazi Jews a "Lost Tribe?"





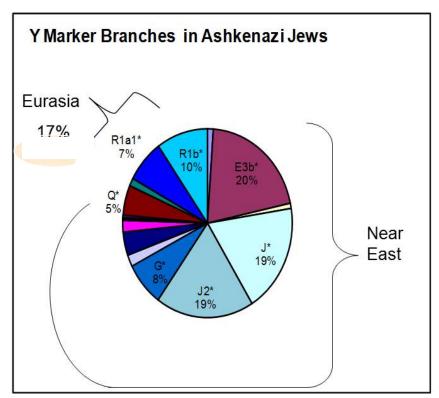


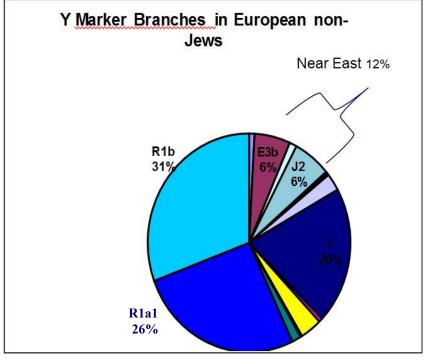




Hammer et al. 2000

Y Chromosome (paternal) Marker Branches in Ashkenazi Jews compared to European non-Jews





Ashkenazi Jews:

Mostly Near East Branches (J, E major founding; G, Q minor founding)

ARTICLE

Received 28 Jun 2013 | Accepted 13 Nov 2013 | Published 17 Dec 2013

DOI: 10.1038/ncomms3928

OPEN

Phylogenetic applications of whole Y-chromosome sequences and the Near Eastern origin of Ashkenazi Levites

The R1a I not of E

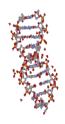
European Non-Jews:

Mostly Eurasian Branches (R1a1, R1b and I) SCIENTIFIC REPORTS

OPEN The genetic variation in the R1a clade among the Ashkenazi Levites'
Y chromosome

Doron M. Behar^{1,2}, Lauri Saag¹, Monika Karmin¹, Meir G. Gover³, Jeffrey D. Wexler⁴, Luisa Fernanda Sanchez², Elliott Greenspan², Alena Kushniarevich^{1,5}, Oleg Davydenko³, Hovhannes Sahakyan¹, Levon Yepiskoposyan⁴, Alessio Boattini⁷, Stefania Sarno⁷, Luca Pagani^{1,8}, Shai Carmi⁸, Shay Tzur^{8,19}, Ene Metspalu^{1,1}, Concetta Bormans², Karl Skorecki^{10,13}, Mait Metspalu¹, Siiri Rootsi¹ & Richard Villems^{1,12}

Chromosome Y Genes



Flipping TV Channels

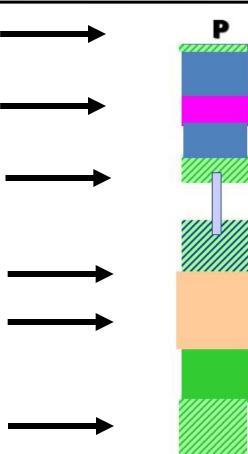
Unwillingness to ask for Directions When Driving

Reluctance to Express Emotions

Memory for Jokes

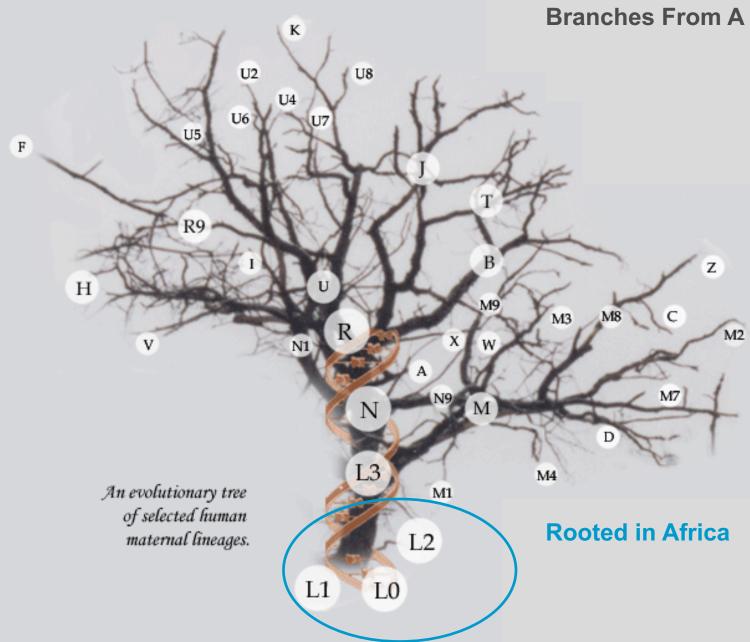
Forgetting Wedding Anniversary dates

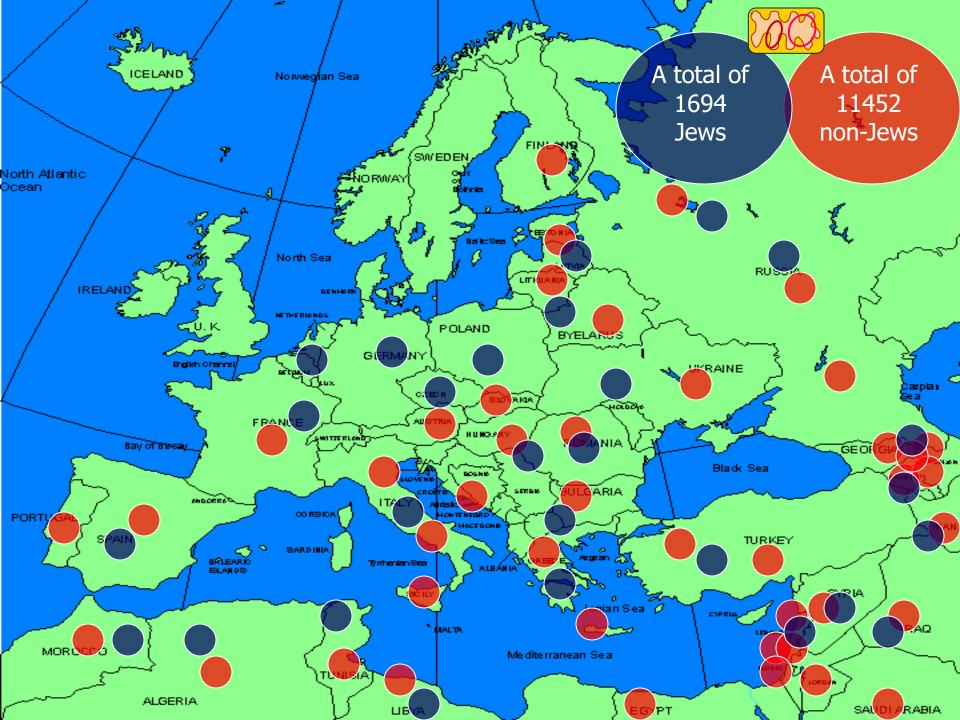
Sports Addiction





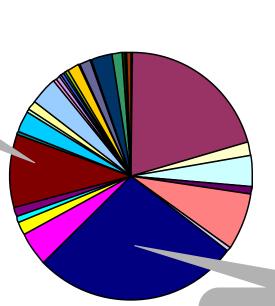
Mitochondrial DNA Marker Branches From A to Z





Four Founding Mothers of Near East Provenance Gave Rise to ~40% of Contemporary Ashkenazi Jews

One exclusive N1b lineage ~10% of Ashkenazi Jews Coalescence: 721 ybp



Three exclusive K lineages 19+7+4% of Ashkenazi Jews Coalescence: 742, 1971, 1971 ybp

These mtDNA haplotypes are of Near East origin

The New York Times

Coppright D 2008 The New York Tires

NEW YORK, SATURDAY, JANUARY 14, 2006

New Light On Origins Of Ashkenazi In Europe

By NICHOLAS WADE

A new look at the DNA of the Ashkenazi Jevish population has thrown light on its still mysterious origins.

Until now, it had been widely assumed by genelicists that the Ashkoness commardiae of Northern and Central Europe were tounded by mee who come from the Middle East, perhaps as traders, and by the A study calls four women the ancestors of 40 percent of Ashkenazi Jews.

women's origins.

David Goldstein, now of Duke University, reported in 3002 that the initrochendrial DNA of women in Jewish communities around the world, did not seem to be Middle Eastern, and indeed coch community had its own genetic pattern. But in some cases the mitochondrial DNA was clearly related to that of the host community.

Dr. Goldstein and his collengues suggested that the genesis of tach Jowish community, including the

Connected by Amy Harmon January 22, 2006

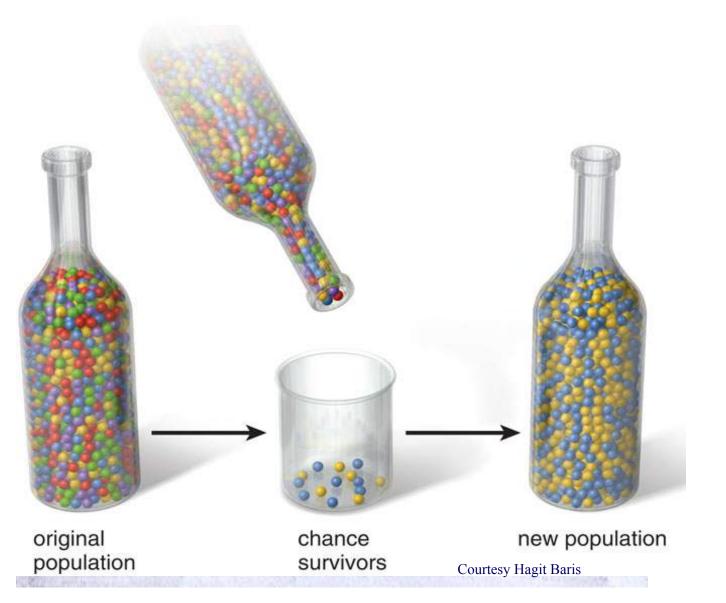
Love You, K2a2a, Whoever You Are



Y and mtDNA both favour bottleneck explanation for

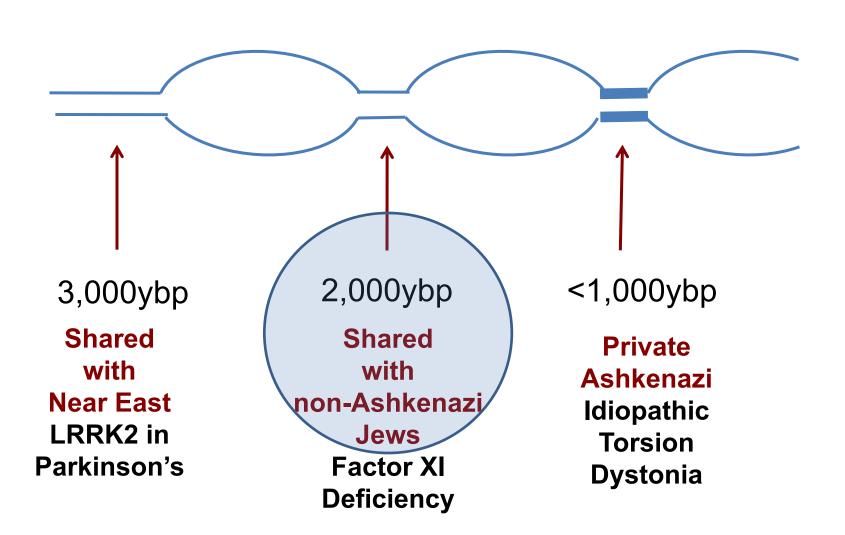
"Ashkenazi" disease alleles

Cystic Fibrosis



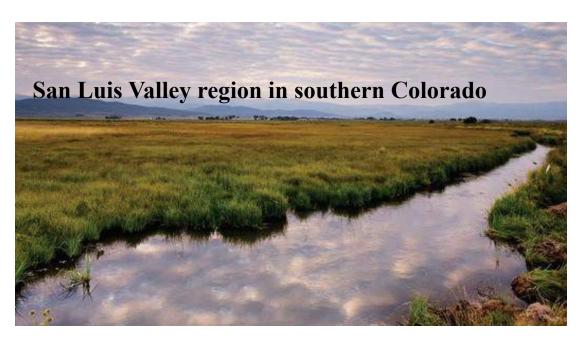
- >1300 mutations worldwide
- Only 6account for95% of CFin AshkenaziJews

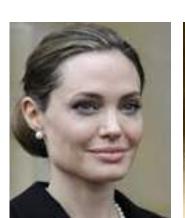
Bottlenecks



The 185delAG *BRCA1* mutation originated before the dispersion of Jews in the Diaspora and is not limited to Ashkenazim

Revital Bruchim Bar-Sade¹, Anna Kruglikova¹, Baruch Modan⁴, Eva Gak², Galit Hirsh-Yechezkel⁴, Livia Theodor¹, Ilya Novikov⁴, Ruth Gershoni-Baruch⁷, Shulamit Risel³, Moshe Z. Papa⁵, Gilad Ben-Baruch⁶ and Eitan Friedman^{1,*}





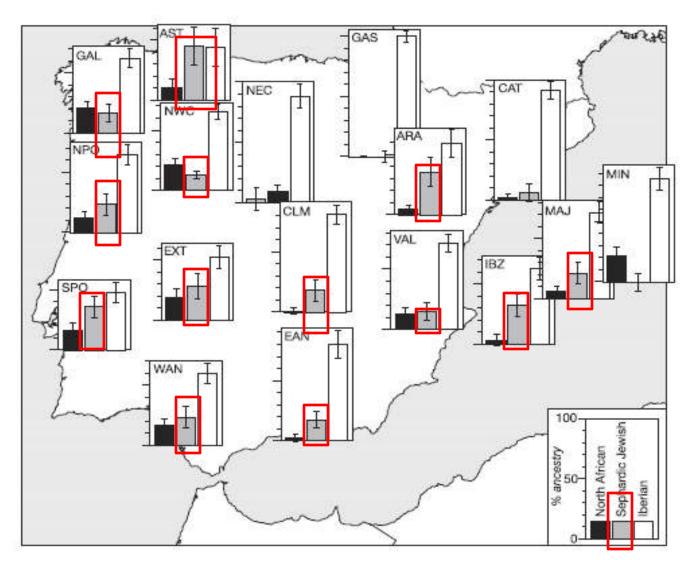


Chromosome 17

Friedman, Ostrer et al. Ashkenazi BRCA1 Mutation 185delAG mutation for breast cancer in New Mexican and southern Colorado and other Hispanic communities



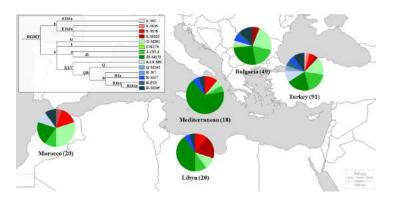
Iberian Peninsula and Balearic Islands



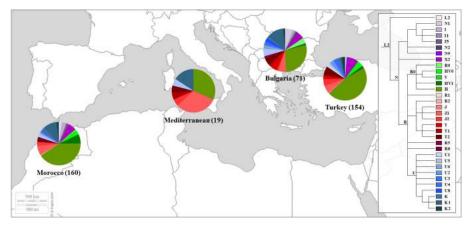
~20% מתושבי חצי האי האיברי כיום הנם ממוצא יהודי

Descendants of the Conversos

Y and mtDNA Haplotypes in Jewish Communities Descendant from Iberian Exile



Y-Chromosome



mtDNA

Noguiero et al. 2015 based on Behar 2008 and Picornell 2006



Chueta of Mallorca were designated as Jewish in 2011 after more than 500 years





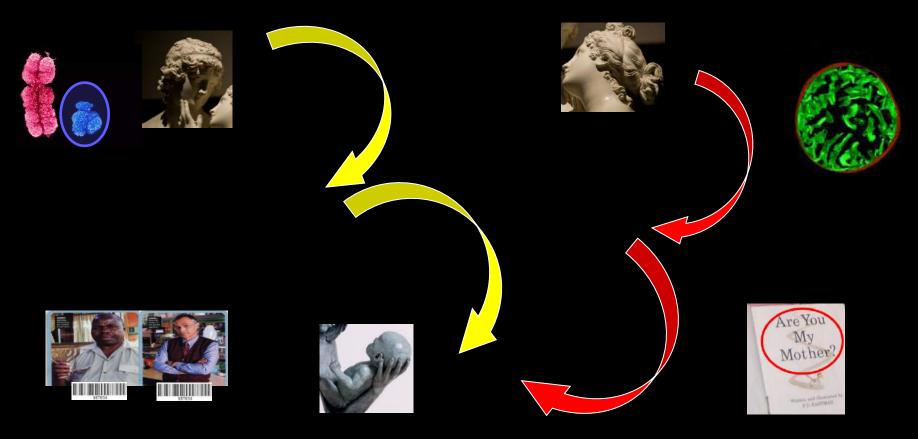


"Lost Tribes and Hidden Jews"

Are we there yet?

Reconstructing Ancestry

Individuals who share the same set of markers for a given DNA region share a common ancestry at that genomic region



If the markers are on the Y-chromosome – shared paternal ancestry

If the markers are on mitochondrial DNA – shared maternal ancestry



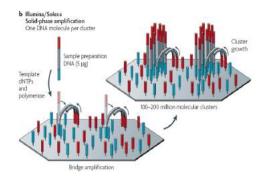




Each individual is a beautiful COMPOSITE of many Ancestors and each Genomic Region has its own evolutionary history

Easily evident in the Whole Genome

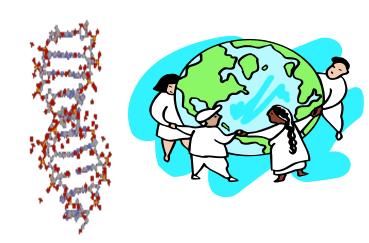
Now technologically, computationally, and economically practical to also study the whole genome





Genome Wide View of World Wide Jewish Diaspora Communities

Genome Wide



14 Diaspora Jewish and more than 60 non-Jewish Communities

- ➤ Western and Eastern Europe: Ashkenazi and Sephardi
- > North Africa
- > Near and Middle East
- India and Far East
- **→** Hidden Communities

doi:10.1038/nature09103

The genome-wide structure of the Jewish people



Doron Behar



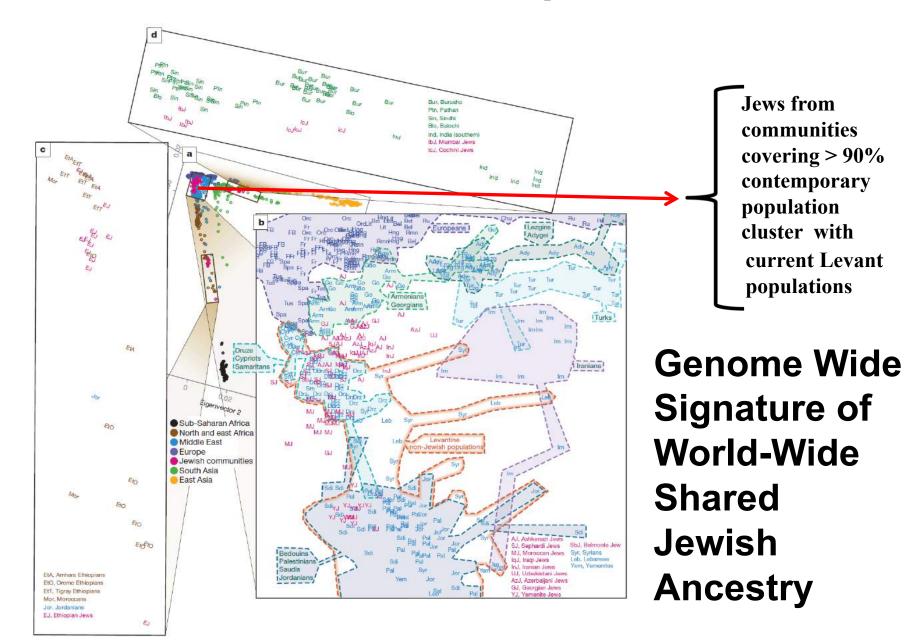
Richard Villems Estonian BioCenter



Shay Tzur Guennady Yudkovsky

Researchers from Eight Countries

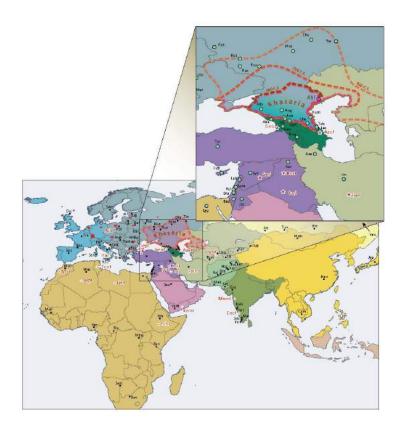
Analysis of 500,000 Genome Wide Markers: 14 Jewish and 69 non- Jewish Populations

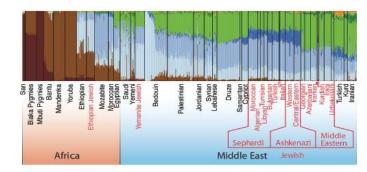


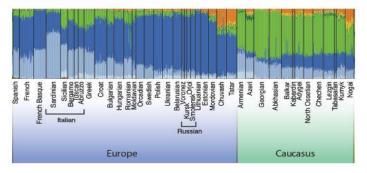
8-1-2013

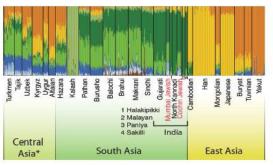
No Evidence from Genome-Wide Data of a Khazar

Origin for the Ashkenazi Jews









Ultimate Resolution → Whole Genome Sequence

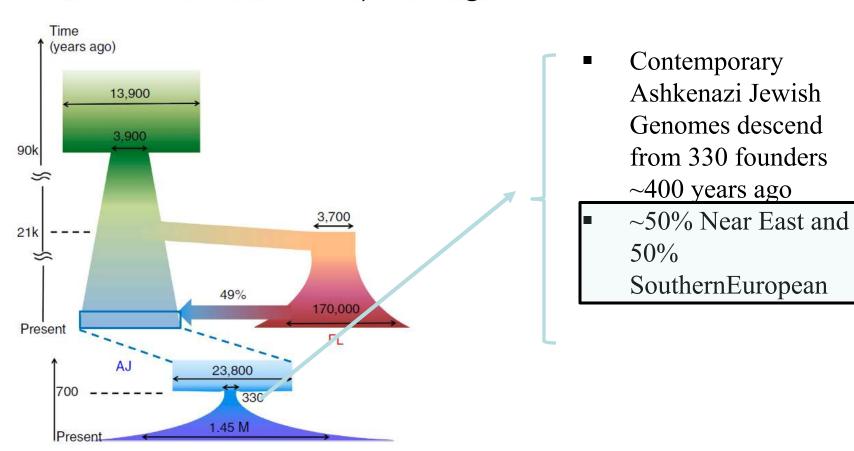
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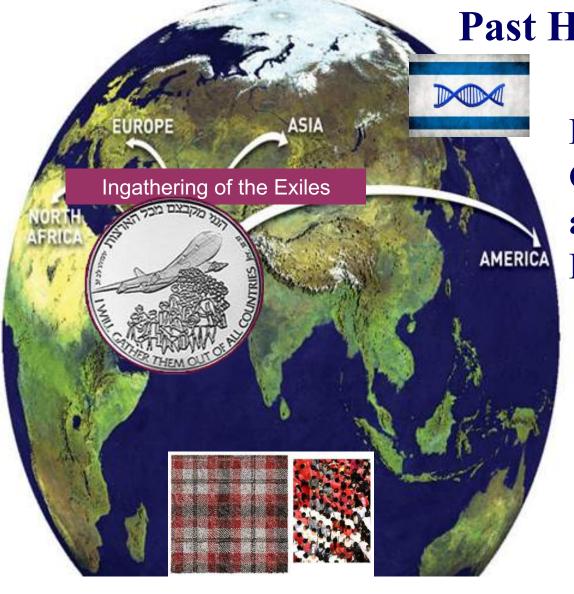
Received 24 Jun 2014 | Accepted 28 Jul 2014 | Published 9 Sep 2014

DOI: 10.1038/ncomms5835

OPEN

Sequencing an Ashkenazi reference panel supports population-targeted personal genomics and illuminates Jewish and European origins Carmi et al 2014





Mosaic or Tapestry?

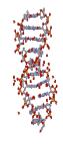
Past History of the Jewi People

Levant Origin with Global Genomic and Cultural Influence

- Introgression
- Conversion
- Admixture
- Evolutionary Adaptation to environment

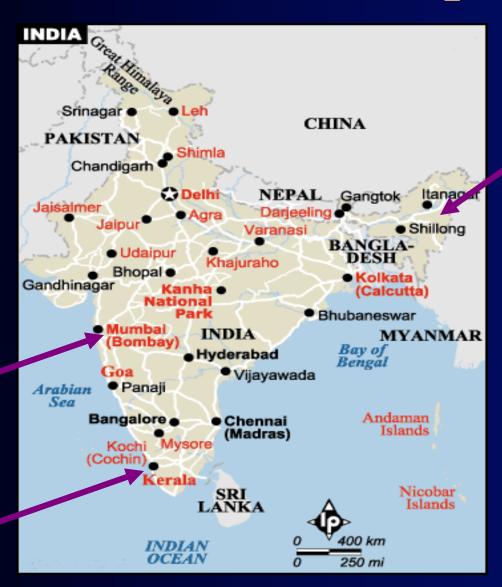
Autumn 2009 – Haaretz supplement





- ➤ Genetics tells us that there is shared Jewish ancestry throughout the globe
- However finding lost Jews extends beyond genetics

Indian Jewish Diaspora

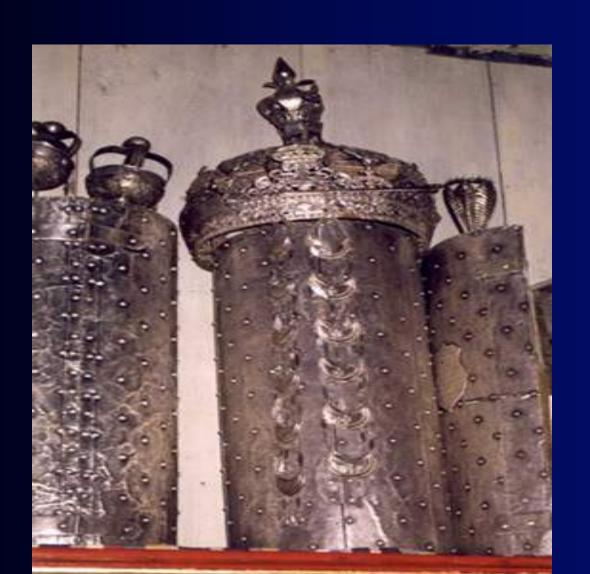


Bene-Menashe

Bene-Israel

Cochin

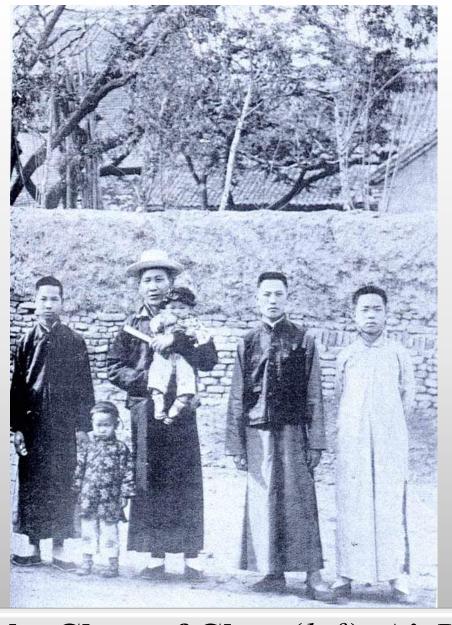
Ancient Cochin Torah Scrolls





Bene Menashe children in a village in northeastern India

אתה בהרתנו מכל העמים ורציתה כנו מפל הלשונות קרשתנו במצותיך וקרבתנו מלכינו לעכורתיך ושמך הגרול והקהוש עלינוקראת:ותתך לנו יהוה אלהינו את יום טול מקרא קורש הזה את יום הזפרון הזה זכרון הרעה באהכה זכר ליציאת מצרים: ומפני חטיינו ללינו מארצנו ונתרחק מעל ארמתינו ואיך אנויכולין לעלות להראות להשתחות לפניך בית



Jews from the Clans of Chao (*left*), Ai, Li, and Shih; K'aifeng Conference, 1919

















Ethiopian Jews (Beta Israel) Low Risk for Kidney Failure

What protects Ethiopian Jews from Kidney Failure?



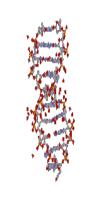
Population Based Health and Disease Gene Discovery



POPULATION BASED GENE MAPPING

Identification of Major Kidney Disease Causative Gene → APOL1







Research progress with industry to target this gene product in preventing and treating the worldwide challenge of kidney and cardiovascular disease

APO-test

- Kidney transplantation
- **Nephrotoxins**
- Antihypertensives













> Changing Genomic Structure in Israeli Jewish Community

> Changing Genomic Structure in U.S. Jewish Community

> Recovery of "Lost Jews" from remote communities



> Changing Genomic Structure in Israeli Jewish Community





קבוץ גלויות 💳 מיזוג גלויות



> Changing Genomic Structure in U.S. Jewish Community





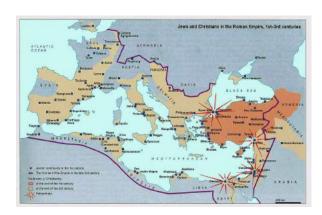
- Egress of Jewish ancestry into general population
- Growth of a few communities with high levels of endogamy







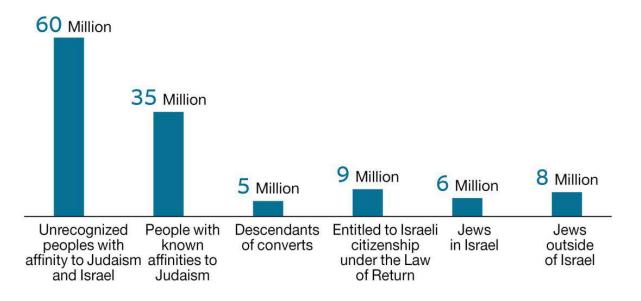
NOT NEW!





> Recovery of "Lost Jews" from remote communities

Number of Jews and people with affinity to Judaism around the world





Michael Freund – Shavei Israel

Source: Diaspora Ministry committee report



> Changing Genomic Structure in Israeli Jewish Community

> Changing Genomic Structure in U.S. Jewish Community

- > Recovery of "Lost Jews" from remote communities
 - > Future of humankind



Context: Genetic Future of Humankind

Hershkovitz et al. Science 2018

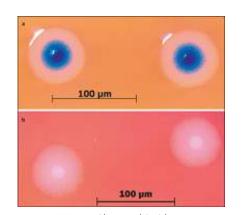
The earliest modern humans outside Africa







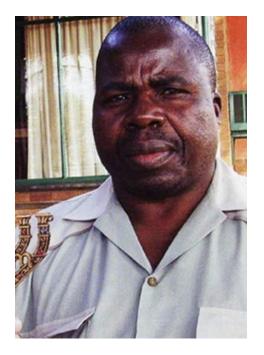
Synthetic Genome

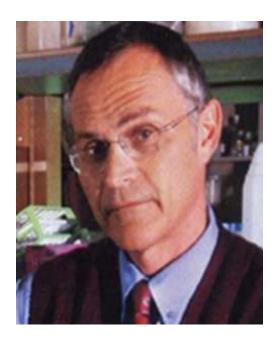


New Life Form



Venter, Glass, and Smith





Societal and Legal Considerations: e.g. Jewish Identity





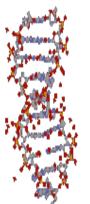
Biology and Jewish Identity

Paul Newman and Peter Lawford
Scholarly Discussion and Experimental Testing of
"Biological Phenotype Hypothesis"





Beyond the Jewish Genome:







Jewish Epigenomics



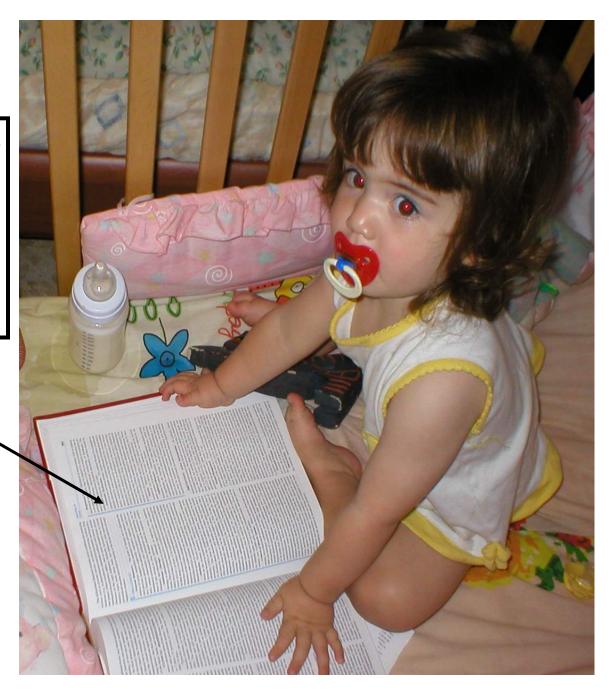
Harrison's 19th edition

Chapter 335

Chronic Kidney

Disease

Nature or Nurture or Epigenome





A Cultural Epigenome



Talmudic view of

"genetic predeterminism"

"Strive to be a student* of Aaron:

love peace and pursue peace".

* student rather than descendant

Hillel: Ethics of the Fathers

Molecular Medicine Laboratory: Looking for Answers







Case 1

30 year old Israeli woman is to marry an Israeli Jewish man in Israel. The woman immigrated at the age 12 from the Ukraine under the "Law of Return". There is documentation for Jewish identity of her paternal grandfather, but no comparable record as her maternal side.

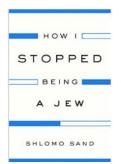
The Rabbinical Courts in Israel refuse to grant a marriage permit. She carries out private DNA testing which shows that her mitochondrial (maternally transmitted) DNA is of the K1a1b1a sublineage shared with 1.5 millions of established Jews, while was found only in one non-Jew(?) subject from west Ukraine in a 13500 non-Jewish European sample set.

Does the woman need conversion?



Am I (Born) Jewish?

- Transcendental feeling
- Tay-Sachs mutation carrier on an incidental screen
- Told by mother on her deathbed that she was born Jewish
- Wanting to be not Jewish







Should I sequence my mitochondrial DNA to help me achieve a greater level of certainty about myself





Mitochondrial DNA – Was I Born Jewish?

Natalia (arrived from former Soviet Union during 90's)

Maayan (combat IDF, granddaughter of Palmach fighter frmom Kibbutz Mishmar HaEmek)

Shaindel (married to Rosh Yehshiva in Bene Beraq)





Anna Svetlana Natalia Shoshana Noa Maayan



Rachele Braindel Shaindel



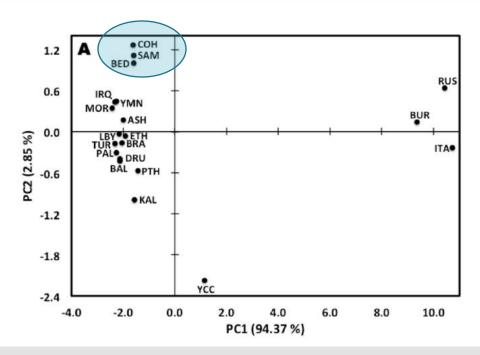












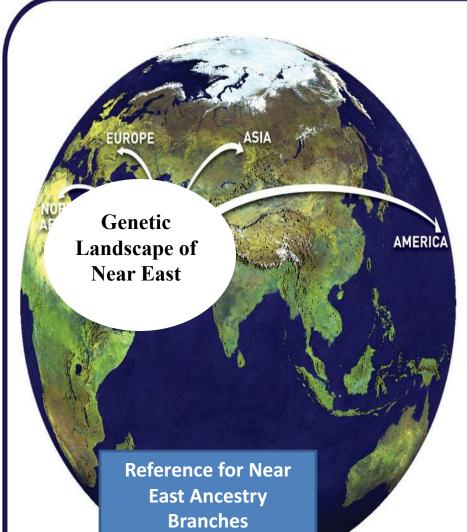
Y chromosome marker (DYS prefix)														
Family	19	388	389-I	389-II	390	391	392	393	426	438	439	YCAIIa	YCAIIb	Haplogroup ³
Cohen-1	14	12	13	18	24	10	11	13	11	10	19	19	22	E3b (M78)
Cohen-2	14	12	13	18	24	11	11	13	11	10	19	19	22	E3b (M78)
Danfi-1	14	15	14	16	24	10	11	12	11	9	18	19	22	J2f (M172, M67)
Danfi-2	14	15	14	16	23	10	11	12	11	9	18	19	22	J2f (M172, M67)
Joshua-Marhiv-1	14	16	13	17	23	11	11	12	11	10	17	22	22	J1 (M267)
Joshua-Marhiv-2	14	16	13	17	23	11	11	12	11	10	17	22	22	J1 (M267)
Joshua-Marhiv-3	14	16	13	17	23	11	11	12	11	10	17	22	22	J1 (M267)
Joshua-Marhiv-4	14	16	13	17	23	11	11	12	11	10	17	22	22	J1 (M267)
Tsedaka-1	14	15	13	16	23	10	11	12	12	8	20	19	22	J2* (M172)
Tsedaka-2	14	15	13	16	23	10	11	12	12	8	20	19	22	J2* (M172)
Tsedaka-3	14	15	13	16	23	10	11	12	12	8	20	19	22	J2* (M172)
Tsedaka-4	14	15	13	16	23	10	11	12	12	8	20	19	22	J2* (M172)
CMH ¹	14	16	13	16	23	10	11	12	11	10	19	22	22	J1 (M267)
CMH ²	14/15	15/16	14	16	23	10	11	12	11	9	19	19	22/23	J2* (M172)
														Oefner et al. 2



העדה הדרוזית היא "שמורת טבע" של המבנה הגנטי של אוכלוסית המזרח התיכון בימים קדומים

Clustered Genome-Wide Ancestry with Ashkenazi and non-Ashkenazi Jews

But the Druze have not wandered the face of the globe



Numerous
Disease Genes
have been
mapped in
both the
Druze and
Jewish
populations

