

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!



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 ?



The Genetic History of the Jewish People Is there a Jewish People ?

Shaye Cohen



Martin Gilbert z"l



Sergio Della Pergola



Tudor Parfitt



Steven Weitzman















- 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

Discovery of DNA

IO

Rosalind Franklin

The Double Helix



DNA Replication

Precise — no errors

boring world full of identical copies of same sequence

Errors ---> richness of living diversity price: illness



RAMBAM Health Care Campus

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



"For man is but the tree of the earth"

Deuteronomy 20:19

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





SCIENTIFIC CORRESPONDENCE

nature

Y chromosomes of Jewish priests

Sin - 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 strict patrilineal descent, Accordingly, we cemetery gravestones, priests represent frequency of Y-chromosome haplotypes male world Jewish population of roughly between Jewish priests and their lay 7 million (data not shown). counterparts. Remarkably, the difference communities.

HAPLOTYPE FREQUENCY Fistandard error Sephardic All Ashkenanic. Cohen Israelite Cohen Israelit Cohen Israelite /=81 1=24 1=39 n=68 r=120 /1=44 0.162 0.091 0.205 0.074 0.083 0.129 10.0450 (0.026) (0.061) (0.029)(0.056) (0.054) 0.544 0.325 0.454 0.321 0.709 0.333 (0.075) (0.052) (0.093) (0.075) (0.060) (0.042) 0.042 0.359 0.162 0.300 0.227 0.272 (0.045) (0.042) (0.063) (0.049)(0.041) (0.077) Karl Skorecki 0.063 0.089 0.083 0.091 0.111 0.026 Sara Selig (0.035) (0.044) (0.035) (0.056) (0.024) (0.024) Shraga Blazer 0.083 0.029 0.017 0.000 0.025 0.000 (0.020) (0.012) (0.017) (0.056) --0.015 0.184 0.023 0.102 0.000 0.153 DVS10 Rambam Medical Centre 10.0351 (0.024) (0.045) (0.057) 0.0149

trast, we found no significant difference in the distribution of alleles for the non-Ychromosome locus polymorphism D1S191 (data not shown). These Y-chromosome

paternal genealogy for Jewish priests. We further identified subjects as being of Ashkenazic or Sephardic origin. This tinues to this day, and is determined by communities. Based on surveys of Jewish refers to the two chief, separate communities 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 Ashkenazie 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 tion12, 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 evo- ther supported by the relative prepondernot 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 ago12; and second, a both populations, suggesting that this may have been the founding modal haplotype 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 chromosomes of Jewish priests during the relatively short time since the establishment of the priesthood, should be useful in defining rates and mechanisms of Ychromosome evolution. Bruce Rappaport Faculty of Medicine and Research institute and

Technion (srae) 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:
 - FamilvtreeDNA
 - **National Genographic**
 - many other



"Lost Tribes and Hidden Jews"



Are They Related?



N

Traditional History of The Lemba



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

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OPEN

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DOI: 10.1038/ncomms3928

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



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 Sanchez¹, Elliott Greenspan³, Alena Kushniarevich^{1,3}, Oleg Davydenko⁵, Hovhannes Sahakyan¹, Levon Yepiskoposyan⁶, Alessio Boattini⁷, Stefania Sarno⁷, Luca Pagani^{1,4}, Shai Carmi⁹, Shay Tzur^{5,10}, Be Metspalu^{1,11}, Concetta Bormans², Kad Skorecki^{10,13}, Mait Metspalu⁰, Siiri Rootsi¹ & Richard Villems^{1,11}

Chromosome Y Genes











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

> These mtDNA haplotypes are of Near East origin

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


Coppright (2000) 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 Ash-

A new low and the birds of the part kenszi sevish population has thrown light on its still mysterious origins. Until now, it had been widely nesumed by geneticities that the Asthenezi communities of Northern land Central Europe were founded by men who came 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 Goldsrein, now of Dake Unvenity, reported in 2002 that the mitochendrical DNA of women in Jewish communities around the world, did not seem to be Middle Eastern, and indeed each community had its own genetic partern. But in some cases the mitochondrial DNA was clearly related to that of the host community.

Dr. Goldstein and his collengues sargested that the genesis of each 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

>1300mutationsworldwide

 Only 6 account for
 95% of CF
 in Ashkenazi
 Jews

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 17q25.2 17q24.3 17q24.3 17q24.1 17q21.32 17q21.32 17q21.2 17q21.2 17q21.2 17q21.2 17q21.2 17q21.2 17q21.2 17q21.2 17q22.2 17q24.1 17q25.2 17q24.1 17q25.2 17q24.1 17q25.2 17q24.1 17q21.2 17q12 17q12



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

Jewish Migration to Europe

Svalbard



Iberian Peninsula and Balearic Islands



~20% מתושבי חצי האי האיברי כיום הנם ממוצא יהודי

Adams et al. AJHG, 2008

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

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



Jews from communities covering > 90% contemporary population cluster with current Levant populations

Genome Wide Signature of World-Wide Shared Jewish Ancestry Behar et al. 2013

WSU Press

8-1-2013

No Evidence from Genome-Wide Data of a Khazar Origin for the Ashkenazi Jews





Ultimate Resolution \rightarrow Whole Genome Sequence

ARTICLE

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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 JewiPeopleLevant Origin withGlobal Genomicand CulturalInfluence

- 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

Ancient Cochin Torah Scrolls





Bene Menashe children in a village in northeastern India





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

1.

2.

3.



Personalized Medicine

Nephrotoxins

Kidney transplantation

Europe



> 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







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



Romesberg

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






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



Many students colleagues and collaborators





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?



- 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 <u>Natalia</u> Shoshana Noa <u>Maayan</u>



Rachele Braindel <u>Shaindel</u>













722 727							marker							
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