

ETHNIC SEPHARDIC JEWS IN THE MEDICAL LITERATURE

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GENETICS – Part a. Populations and Ethnic Discussion**The correlation between languages and genes: the Usko-Mediterranean peoples.**

Arnaiz-Villena A; Martinez-Laso J; Alonso-Garcia J; *Human Immunology*. 2001 Sep;62(9):1051-61. U.S. / English

Abstract: The usko-Mediterraneans peoples are defined as ancient and present day populations that have lived in the Mediterranean/Middle-East/Caucasus area and have spoken a Basque related language. The present day existing populations show an HLA genetic relatedness which is more or less close according to geographical distance. The Greek sample is an outlying in all genetic analyses, because Greeks have a significant genetic input from sub-Saharan Ethiopians and Blacks. This probably occurred in Pharaonic times. Present day comparisons between genes and languages show a lack of correlation: Macedonian, Palestinians, Kurds, part of Berbers, Armenians, and Turks belong to the old Mediterranean substratum, but they do not speak a language included in the old Mediterranean Dene-Caucasian group. This is due to an “elite”-imposed culture and language. Other ethnic groups speak an “old Mediterranean language” or “usko-Mediterranean language” modified by Roman Latin (i.e., Spanish, Italians), or by other not fully explained processes (Jews). Therefore, the correlation between genes and languages may exist at a macrogeographical level, but not when more precise microgeographical studies are done, as shown in the present “usko-Mediterranean” peoples model. ❖

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

Bar-Sade RB; Kruglikova A; Modan B; Gak E; Hirsh-Yechezkel G; Theodor L; et al. *Human Molecular Genetics*. 1998 May;7(5):801-5. U.K. / English

Abstract: The 185delAG mutation in BRCA1 is detected in Ashkenazi Jews both in familial breast and ovarian cancer and in the general population. All tested Ashkenazi mutation carriers share the same allelic pattern at the BRCA1 locus. Our previous study showed

that this 'Ashkenazi' mutation also occurs in Iraqi Jews with a similar allelic pattern. We extended our analysis to other non-Ashkenazi subsets: 354 of Moroccan origin, 200 Yemenites and 150 Iranian Jews. Heteroduplex analysis complemented by direct DNA sequencing of abnormally migrating bands were employed. Four of Moroccan origin (1.1%) and none of the Yemenites or Iranians was a carrier of the 185delAG mutation. BRCA1 allelic patterns were determined for four of these individuals and for 12 additional non-Ashkenazi 185delAG mutation carriers who had breast/ovarian cancer. Six non-Ashkenazi individuals shared the common 'Ashkenazi haplotype', four had a closely related pattern, and the rest (n = 6) displayed a distinct BRCA1 allelic pattern. We conclude that the 185delAG BRCA1 mutation occurs in some non-Ashkenazi populations at rates comparable with that of Ashkenazim. The majority of Jewish 185delAG mutation carriers have a common allelic pattern, supporting the founder effect notion, but dating the mutation's origin to an earlier date than currently estimated. However, the different allelic pattern at the BRCA1 locus even in some Jewish mutation carriers, might suggest that the mutation arose independently. ❖

Sephardic Jews in Germany.

Bernstein ME. *American Journal of Human Genetics*. 1993 Aug; 53(2): 532 U.S. / English [N.A.] ❖

Ethnic communities in Israel: the genetic blood markers of the Moroccan Jews.

Bonne-Tamir B; Ashbel S; Bar-Shani S. *American Journal of Physical Anthropology*. 1978 Nov;49(4):465-71. U.S. / English

Abstract: One hundred and ninety-six Moroccan Jews now settled in Israel were typed for 7 blood groups, 12 red cell enzymes and 2 plasma protein systems. Their blood group picture is in agreement with results previously obtained on different samples of Moroccan Jews: rather high B in ABO, somewhat elevated frequencies of cDe and cDE in Rh and K in Kell. Differences in various blood markers exist between them and other North African Jewish communities. This fact, together with data on disease distribution and HLA

frequencies, supports our assumption that Jews in the North African diaspora lived as small secluded isolates even within the same geographical zones. Comparisons with meager data on the neighboring non-Jewish populations do not disclose any resemblance to either Arab or Berber inhabitants of Morocco. ❖

Human mitochondrial DNA sequence variation in the Moroccan population of the Souss area.

Brakez Z; Bosch E; Izaabel H; Akhayat O; Comas D; Bertranpetit J; et al. *Annals of Human Biology*. 2001 May-Jun; 28(3): 295-307 U.K. / English

BACKGROUND: Various populations have contributed to the present-day gene pool of Morocco, including the autochthonous Berber population, Phoenicians, Sephardic Jews, Bedouin Arabs and sub-Saharan Africans. **OBJECTIVE:** The primary objective of the study was to complete a genetic description of the Berber-speaking population in the Souss region of southern Morocco, based on mitochondrial DNA (mtDNA) sequence analysis. **SUBJECTS AND METHODS:** The first hypervariable segment of the mtDNA control region was sequenced in a sample of 50 individuals from the Souss Valley, and the results compared with the extensive body of data available on mtDNA sequence variation in Europe and sub-Saharan Africa. **RESULTS:** Thirty-four different sequences were found: an estimated 68% of the sequences occurred throughout Europe, West Asia and North Africa, 26% originated in sub-Saharan Africa, and 6% belonged to the North African specific haplogroup U6. The Souss Valley mtDNA sequences indicated the presence of two populations which expanded at different times: the West Eurasian sequences in the Souss sample had a smaller average number of pairwise differences than pairs of sub-Saharan sequences. **CONCLUSION:** Detailed knowledge of the possible geographic origin of each sequence facilitated an interpretation of both internal diversity parameters and between-population relationships. The sub-Saharan admixture in the Souss Valley matched the south-north cline of sub-Saharan influence in North Africa, also evident in the genetic distances of North African populations to Europeans and sub-Saharan Africans. ❖

The phylogeography of Brazilian Y-chromosome lineages.

Carvalho-Silva DR; Santos FR; Rocha J; Pena SD. *American Journal of Human Genetics* 2001 Jan;68(1):281-6.. U.S. / English

Abstract: We examined DNA polymorphisms in the nonrecombining portion of the Y-chromosome to investigate the contribution of distinct patrilineages to the present-day white Brazilian population. Twelve unique-event polymorphisms were typed in 200 unrelated males from four geographical regions of Brazil and in 93 Portuguese males. In our Brazilian sample, the vast majority of Y-chromosomes proved to be of European origin. Indeed, there were no significant differences when the haplogroup frequencies in Brazil and Portugal were compared by means of an exact test of population differentiation. Y-chromosome typing was quite sensitive in the detection of regional immigration events. Distinct footprints of Italian immigration to southern Brazil, migration of Moroccan Jews to the Amazon region, and possible relics of the 17th-century Dutch invasion of northeast Brazil could be seen in the data. In sharp contrast with our mtDNA data in white Brazilians, which showed that > or =60% of the matrilineages were Amerindian or African, only 2.5% of the Y-chromosome lineages were from sub-Saharan Africa, and none were Amerindian. Together, these results configure a picture of strong directional mating between European males and Amerindian and African females, which agrees with the known history of the peopling of Brazil since 1500. ❖

Strong Amerind/white sex bias and a possible Sephardic contribution among the founders of a population in northwest Colombia.

Carvajal-Carmona LG; Soto ID; Pineda N; Ortíz-Barrientos D; Duque C; Ospina-Duque J; et al. *American Journal of Human Genetics*. 2000 Nov; 67(5): 1287-95 U.S. / English

Abstract: Historical and genetic evidences suggest that the recently founded population of Antioquia (Colombia) is potentially useful for the genetic mapping of complex traits. This population was established in the 16th-17th centuries through the admixture of Amerinds, Europeans, and Africans and grew in relative isolation

until the late 19th century. To examine the origin of the founders of Antioquia, we typed 11 markers on the nonrecombining portion of the Y chromosome and four markers on mtDNA in a sample of individuals with confirmed Antioquian ancestry. The polymorphisms on the Y chromosome (five biallelic markers and six microsatellites) allow an approximation to the origin of founder men, and those on mtDNA identify the four major founder Native American lineages. These data indicate that approximately 94% of the Y chromosomes are European, 5% are African, and 1% are Amerind. Y-chromosome data are consistent with an origin of founders predominantly in southern Spain but also suggest that a fraction came from northern Iberia and that some possibly had a Sephardic origin. In stark contrast with the Y-chromosome, approximately 90% of the mtDNA gene pool of Antioquia is Amerind, with the frequency of the four Amerind founder lineages being closest to Native Americans currently living in the area. These results indicate a highly asymmetric pattern of mating in early Antioquia, involving mostly immigrant men and local native women. The discordance of our data with blood-group estimates of admixture suggests that the number of founder men was larger than that of women. ❖

Dating the origin of the V170M mutation causing non-type I cystinuria in Libyan Jews by linkage disequilibrium and physical mapping of the SLC7A9 gene.

Colombo R. *Genomics*. 2000 Oct 1;69(1):131-4. U.K. / English

Cystinuria is an autosomal recessive disorder of the transepithelial transport of amino acids, clinically manifested by the development of kidney stones [...] The estimated age dates the most recent common ancestor of the mutation-bearing chromosomes back to the time (or some decades before) Jewish families settled in Libya following their expulsion from the Iberian Peninsula. This finding makes the molecular population genetics of cystinuria understandable in the context of the Libyan Jews' history. [A.T.] ❖

HLA polymorphism in a Majorcan population of Jewish descent: comparison with Majorca, Minorca, Ibiza (Balearic Islands) and other Jewish communities.

Crespi C; Mila J; Martinez-Pomar N; Etxagibel A; Munoz-Saa I; Priego D, et al. *Tissue Antigens*. 2002 Oct;60(4):282-91. English

Abstract: 'Chueta' was the name given to the Catholic descendants of Jewish victims of the last Spanish Inquisition process in Majorca Island in the western Mediterranean. We have studied the allele distribution of HLA-A, -B, -Cw, -DRB1 and -DQB1 loci of 103 random, healthy, unrelated individuals belonging to the ancient Majorcan Jewish community, known locally as Chuetas, and 589 individuals from the Balearic population selected because of their typical Balearic - Majorca, Minorca or Ibiza - lineages and according to their ancestor's place of birth. Our aim was to establish the genetic relationship between Majorcan Chuetas, and Balearic and other Jewish and Mediterranean populations. Our results have shown that, to a remarkable extent, they have retained their biological identity, with a unique pattern, in terms of gene and haplotype frequencies, separate from the other populations of Majorca. The Chuetas were found to be more related to Moroccan and Libyan Jews than other Majorcans. Characteristic Jewish haplotypes, A26-B38-DRB1*13, A24-B38-DRB1*11, A1-B52-DRB1*15/16, were found in our study. Some peculiarities were observed in the distribution of common haplotypes among the three main Balearic Islands. The Ibizan population was genetically different from the other Balearic populations, with a high frequency of some haplotypes, for example, A29-Cw*16-B44-DRB1*07-DQB1*03; A1-Cw*07-B8-DRB1*03-DQB1*02. We also found a new haplotype, A25-Cw*12-B39-DRB1*11-DQB1*03(3.5%), in Ibizans and a more limited variability in the HLA alleles that were expressed, perhaps because of genetic isolation. The genetic diversity of the populations from Majorca and Minorca were similar and more related to the mainland Spanish population. ❖

Population genetic studies on Jews. I. The alpha 2HS serum glycoprotein, a polymorphism strongly correlated with latitude.

Domenici R; Spinetti I; Bargagna M; Morpurgo GP; Levi M; Bar-Shanny S; et al. *Gene Geography: A Computerized Bulletin on Human Gene Frequencies*. 1990 Aug; 4(2): 99-111 Italy / English

Abstract: A sample of Jews subdivided according to the birth-place of their parents or grand-parents have been examined for a large number of genetic markers in the course of a long-term project on the genetics of Jews. We report here the findings concerning 794 Jews studied for the AHSG polymorphism. All the subsamples were in Hardy-Weinberg equilibrium. A highly significant difference was found between Sephardic + Near East Jews and Ashkenazi (AHSG*2 frequencies: 0.184 +/- 0.015 and 0.258 +/- 0.016, respectively). For comparative purposes the data available on Caucasoids have been considered. It turned out that they were neatly arranged along a latitude-AHSG gene frequency cline (0.0092 of AHSG*2 gene frequency increase per degree of increase of latitude) in the explored 30 degrees-60 degrees range ($r = 0.97$; P much less than 0.001). Of the two Jewish frequencies that could be taken into consideration because of their sufficient sizes, that of the Near East + Sephardic Jews was perfectly in line with the above mentioned cline, while that of the Ashkenazi was somewhat displaced in the sense of being more similar than expected to the other, more southern, Jewish group. Since the only AHSG*2 frequency significantly displaced from the regression line is that of the Ashkenazi, whose ancestors lived until centuries ago in more southern areas, this finding is a strong confirmation of the observed cline. ❖

Some effects on the offspring of uncle-niece marriage in the Moroccan Jewish community in Jerusalem.

Fried K; Davies AM. *American Journal of Human Genetics*. 1974 Jan;26(1):65-72. [N.A.] ❖

The photoreceptor cell-specific nuclear receptor gene (PNR) accounts for retinitis pigmentosa in the Crypto-Jews from Portugal (Marranos), survivors from the Spanish Inquisition.

Gerber S; Rozet JM; Takezawa SI; dos Santos LC; Lopes L; Gribouval O; et al. *American Journal of Human Genetics*. 2000 Sep;107(3):276-84.

Abstract: The last Crypto-Jews (Marranos) are the survivors of Spanish Jews who were persecuted in the late fifteenth century, escaped to Portugal and were forced to convert to save their lives.

Isolated groups still exist in mountainous areas such as Belmonte in the Beira-Baixa province of Portugal. We report here the genetic study of a highly consanguineous endogamic population of Crypto-Jews of Belmonte affected with autosomal recessive retinitis pigmentosa (RP). A genome-wide search for homozygosity allowed us to localize the disease gene to chromosome 15q22-q24 ($Z_{\max}=2.95$ at $\theta=0$ at the D15S131 locus). Interestingly, the photoreceptor cell-specific nuclear receptor (PNR) gene, the expression of which is restricted to the outer nuclear layer of retinal photoreceptor cells, was found to map to the YAC contig encompassing the disease locus. A search for mutations allowed us to ascribe the RP of Crypto-Jews of Belmonte to a homozygous missense mutation in the PNR gene. Preliminary haplotype studies support the view that this mutation is relatively ancient but probably occurred after the population settled in Belmonte. ❖

HLA-DRB1 and DQB1 polymorphisms in southern France and genetic relationships with other Mediterranean populations.

Gibert M; Reviron D; Mercier P; Chiaroni J; Boetsch G; *Human Immunology*. 2000 Sep;61(9):930-6. U.S. / English

Abstract: This study presents the results of HLA-DRB1 and DQB1 sequence-specific oligonucleotide probe (SSOP) typing for a population sample of 181 individuals originating from southern France. On the basis of allele and haplotype frequencies, we compared our population with others from the Mediterranean area. Allele frequencies are comparable to those found in other western European populations (France, Portugal, Spain) and indicate neighboring exchanges. The haplotype frequencies showed relationships with North Africans and Jewish populations, as well as the common origin of Moroccan and Lebanese Jews. Therefore, allele frequencies seem to be more able to show recent exchanges while haplotype frequencies might show ancestral relationships. These results may serve as references for future studies of HLA and disease in southern France. ❖

Phosphoglycolate phosphatase in several population groups in Israel.

Golan R; Ben-Ezzer J; Szeinberg A. *Human Heredity*. 1981;31(2):89-92. U.S. / English

Abstract: The genetic polymorphism of phosphoglycolate phosphatase (PGP) found in red blood cells has been investigated in several population groups in Israel: Ashkenazi Jews, non-Ashkenazi Jews from Iraq, Yemen, Turkey, Iran, Balkan, North Africa and Arabs. The distribution of the PGP genes was not homogeneous ($\chi^2 = 40.545$; d.f. = 20; p less than 0.005). The PGP2 gene frequency varied between 0.0185 in the Yemenite and 0.0688 in the Iranian Jews. PGP3 gene frequency ranged between 0.0062 in the Iranian and 0.0547 in the Moroccan Jews. Despite this heterogeneity all the Israeli population groups showed some unifying characteristics which differentiated them from a random European population sample, namely higher frequencies of PGP1 gene (92-97% as opposed to 82% in the European sample) and lower frequencies of PGP2 gene (1.8-6.8% compared to 12.9% among Europeans). ❖

Y-chromosome lineages from Portugal, Madeira and Acores record elements of Sephardim and Berber ancestry.

Goncalves R; Freitas A; Branco M; Rosa A; Fernandes AT; Zhivotovsky LA; et al. *Annals of Human Genetics* 2005 Jul;69(Pt 4):443-54. U.K. / English

A total of 553 Y-chromosomes were analyzed from mainland Portugal and the North Atlantic Archipelagos of Acores and Madeira, in order to characterize the genetic composition of their male gene pool. A large majority (78-83% of each population) of the male lineages could be classified as belonging to three basic Y chromosomal haplogroups, R1b, J, and E3b. While R1b, accounting for more than half of the lineages in any of the Portuguese sub-populations, is a characteristic marker of many different West European populations, haplogroups J and E3b consist of lineages that are typical of the circum-Mediterranean region or even East Africa. The highly diverse haplogroup E3b in Portuguese likely combines sub-clades of distinct origins. The present composition of the Y

chromosomes in Portugal in this haplogroup likely reflects a pre-Arab component shared with North African populations or testifies, at least in part, to the influence of Sephardic Jews. In contrast to the marginally low sub-Saharan African Y chromosome component in Portuguese, such lineages have been detected at a moderately high frequency in our previous survey of mtDNA from the same samples, indicating the presence of sex-related gene flow, most likely mediated by the Atlantic slave trade. ❖

Y-chromosome lineages in Cabo Verde Islands witness the diverse geographic origin of its first male settlers.

Gonçalves R; Rosa A; Freitas A; Fernandes A; Kivisild T; Villems R; et al. *Human Genetics*. 2003 Nov; 113(6): 467-72 Germany / English

Abstract: The Y-chromosome haplogroup composition of the population of the Cabo Verde Archipelago was profiled by using 32 single-nucleotide polymorphism markers and compared with potential source populations from Iberia, west Africa, and the Middle East. According to the traditional view, the major proportion of the founding population of Cabo Verde was of west African ancestry with the addition of a minor fraction of male colonizers from Europe. Unexpectedly, more than half of the paternal lineages (53.5%) of Cabo Verdeans clustered in haplogroups I, J, K, and R1, which are characteristic of populations of Europe and the Middle East, while being absent in the probable west African source population of Guiné-Bissau. Moreover, a high frequency of J* lineages in Cabo Verdeans relates them more closely to populations of the Middle East and probably provides the first genetic evidence of the legacy of the Jews. In addition, the considerable proportion (20.5%) of E3b(xM81) lineages indicates a possible gene flow from the Middle East or northeast Africa, which, at least partly, could be ascribed to the Sephardic Jews. In contrast to the predominance of west African mitochondrial DNA haplotypes in their maternal gene pool, the major west African Y-chromosome lineage E3a was observed only at a frequency of 15.9%. Overall, these results indicate that gene flow from multiple sources and various sex-specific patterns have been important in the formation of the genomic diversity in the Cabo Verde islands. ❖

**Molecular analysis of HLA-B27 haplotypes in Caucasoids.
Frequencies of B27-Cw in Jewish and Spanish populations.**

Gonzalez-Roces S; Brautbar C; Pena M; Dominguez O; Coto E; Alvarez V; et al. *Human Immunology*. 1994 Oct;41(2):127-34. U.S. / English

Abstract: PCR in combination with SSO probes was used to analyze the polymorphism in exons 2 and 3 of HLA-B27 subtypes and HLA-C-related alleles in two genetically distant Caucasian groups: Spanish and Jewish populations. AS patients and healthy B27 donors from both populations were analyzed in order to ascertain B27-Cw haplotypes. Three different ancestral haplotypes were found to be represented in both populations: B*2705/Cw*0102, B*2705/Cw*02022, and B*2702/Cw*02022. The B*2705 (92.5%) was the most frequent allele found in the Spanish population, carried by B*2705/Cw*0102 (60.9%) and B2705/Cw*02022 (30.4%) haplotypes. In contrast, B*2702 (59.4%) was the most prevalent allele found in the Jewish population and was carried by the B*2702/Cw*02022 (63.3%) haplotype. No different allelic and haplotypic distributions were among healthy and AS patients in either Spanish or Jewish populations. The differences found in the distribution of B27 haplotypes among Spanish and Jewish Caucasian populations are consistent with the genetic distance of these ethnic groups. When the Jewish population was subdivided into Ashkenazi (A) and non-Ashkenazi (NA) groups, no significant differences were observed in the distribution of B*2702/Cw*02022 haplotype. Minor differences were observed in the underrepresented B*2705 haplotypes. The present results reflect the ancestral affinities of A and NA Jewish populations. A possible HLA-B27 evolutive pathway in Caucasians is proposed according to the data available for the B27/Cw ancestral haplotypes in Spanish and Jewish groups. ❖

**The genetic structure of Mexican Mestizos of different locations:
tracking back their origins through MHC genes, blood group
systems, and microsatellites.**

Gorodezky C; Alaez C; Vazquez-Garcia MN; de la Rosa G; Infante E; Balladares S; et al. *Human Immunology*. 2001 Sep;62(9):979-91. U. S. English

Abstract: Mexican Mestizos, who are the result of the admixture of Spanish, Indian, and Black genes, were analyzed for different systems. Three populations from geographical distinct areas were studied: the north (State of Nuevo Leon), the center (State of Guanajuato), and the highlands (mainly Mexico City). Ten blood group systems (N = 229), STRs (N = 107), HLA-A*, B*, C* (N = 116-167), and DRB1, DQA1, and DQB1 (N = 40, 101, 160, respectively) were analyzed in the samples of the highlands. The three groups cluster together in the same branch: Mestizos from Venezuela, Mediterranean and Jews close to the cluster of Orientals, followed by Amerindians. All markers demonstrate that Indian genes are strongly represented in the highlands: Di(a), O, D(-)(+), s, A*0201, *0206, B*1539 (*1541), *3902, *3905, *3512, *3517, *4002, *4005, Cw*0801, *0304, *0401 among others. Cw*0501, *1203, *1204, and *1601 are of White ancestry. The most frequent haplotypes *0407-*03011-*0302 and *0802-*0401-*0402 are of Indian descent as well. The center and mainly the north show a more Caucasian and Semitic profile. The results demonstrate the high variability resulting from interethnic admixture, suggesting that this mechanism is the main factor responsible for the large diversity found in urban populations. ❖

LIMITED SAMPLE