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ORIGINAL INVESTIGATION

The impact of *Converso* Jews on the genomes of modern Latin Americans

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Abstract Modern day Latin America resulted from the encounter of Europeans with the indigenous peoples of the Americas in 1492, followed by waves of migration from Europe and Africa. As a result, the genomic structure of present day Latin Americans was determined both by the genetic structure of the founding populations and the numbers of migrants from these different populations. Here, we analyzed DNA collected from two well-established communities in Colorado (33 unrelated individuals) and Ecuador (20 unrelated individuals) with a measurable prevalence of the *BRCA1* c.185delAG and the *GHR* c.E180 mutations, respectively, using Affymetrix Genome-wide Human SNP 6.0 arrays to identify their ancestry. These mutations are thought to have been brought to these communities by Sephardic Jewish progenitors. Principal component analysis and clustering methods were employed to determine the genome-wide patterns of continental ancestry within both populations using single nucleotide polymorphisms, complemented by determination of Y-chromosomal and mitochondrial DNA haplotypes. When examining the presumed *European* component of these two communities, we demonstrate enrichment for Sephardic Jewish ancestry not only for these mutations, but also for other segments as well. Although comparison of both groups to a reference Hispanic/Latino population of Mexicans demonstrated proximity and similarity to other modern day communities derived from a European and Native American two-way admixture, identity-by-descent and Y-chromosome mapping demonstrated signatures of Sephardim in both communities. These findings are consistent with historical accounts of Jewish migration from the realms that comprise modern Spain and Portugal during the Age of Discovery. More importantly, they provide a rationale for the occurrence of mutations typically associated with the Jewish Diaspora in Latin American communities.

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Introduction

For many years, there have been attempts to characterize the nature of the communities of the Jewish Diaspora,

including the predominant genome-wide modalities that have revolutionized the study of genetics for global populations (International HapMap 2003; Atzmon et al. 2010). Among these attempts has been the identification of several Mendelian mutations and diseases that are over-represented in Jewish Diaspora communities, such as breast and ovarian cancer mutation, *BRCA1* c.185delAG (Bar-Sade et al. 1998; Friedman et al. 1995; Oddoux et al. 1996; Struewing et al. 1995), Laron dwarfism growth hormone receptor mutation, *GHR* c.E180 (Laron et al. 1966), and Bloom syndrome mutation, blm^{ash} (German et al. 1977) (for review, see Ostrer 2001). Given the overwhelming prevalence of these mutations and/or diseases in Diaspora communities, it may initially seem surprising to connect these specific mutations to non-Jewish Hispanic/Latino groups (Ah Mew et al. 2002; Bordenave et al. 2001; Ellis et al. 1998; John et al. 2007; Makriyianni et al. 2005; Mullineaux et al. 2003; Rosenbloom and Guevara-Aguirre 2008). However, when one reflects on the history of Jews in the realms of the Iberian Peninsula that would colonize Latin America, the Jewish origin of these mutations becomes more plausible.

The Jews who would become known as the *Sephardim* had a millennial history in Iberia that originated in Classical Antiquity with alternating periods of relative tolerance and total discrimination that culminated with the forced expulsions and conversions that entirely excised this integral community from mainstream Iberian civilization in the 16th to 17th centuries (Prinz 1973). At the same time, the New World was being colonized by Spain and Portugal. The descendants of the Sephardim of this era became to be known by a plethora of terms, of which *Converso* is the preferred term. Conversos were Jews (or Muslims) that had converted to Christianity, specifically its Catholic variant, very often in the setting of discriminatory pressure or outright persecution. However, even without Inquisitorial or government pressure, there were many powerful factors working against coherent maintenance of Jewish orthodoxy and essentially none in favor of its successful transmission; the consequences were either the inheritance of disjointed relics of Jewish ritual or total abandonment and integration with the rest of the Catholic colonial society (Rowland 2001).

Given this rich history and mutation data, it is natural to study the remnant of this Converso heritage among the peoples of Latin America. Here, we focus on two distinct communities that provide a useful lens to examine the impact that Conversos had on the genetic structure of modern day Latin Americans and their descendants around the world. One community in the US Southwest resided in the San Luis Valley of Colorado and will be referenced as *Hispanos* (Hordes 2005; Ordóñez-Chiriboga 2005). Another community resided in the Loja province of Ecuador and will be referenced as *Lojanos* (Ordóñez-Chiriboga 2005). Although there are individuals that strenuously refute the Jewishness of such communities (Sutton et al. 2006), there is evidence of Converso ancestry in communities within or with roots in Latin America. When comparing studies that examine the relationship of Sephardim with other global Jewish populations with those surveys of the Iberian Peninsula and Latin America, it becomes clear that not only can Sephardim be reliably distinguished from other Jewry, but that the basis for this difference can be detected in modern Iberian and Latin American populations (Adams et al. 2008; Atzmon et al. 2010; Bryc et al. 2010; Goncalves et al. 2005; Pacheco et al. 2005).

It has been hypothesized that both communities differ from other Latin American communities in their relative isolation from the colonial and religious authorities, an isolation that made the modern US Southwest (i.e. the sparsely populated north of the Spanish Viceroyalty of New Spain) and southern Ecuador (i.e. the sparsely populated elevated regions of the Spanish Viceroyalty of Peru) natural destinations for Converso migration (Hordes 2005; Ordóñez-Chiriboga 2005). Such an hypothesis was tested when comparing Hispanos and Lojanos with a Latin American population derived from urban Guadalajara, Mexico (Nelson et al. 2008), an important colonial center less remote than these other two locales during the Spanish Imperial Era whose inhabitants less likely experienced a Converso *Frontier Phenomenon*. Given the increasing importance of genomics in the study of disease of complex inheritance, this work becomes critical to the appreciation of the complexity of the foundation not only of the Hispanos and the Lojanos, but also of Latin Americans as a whole.

Results

Diaspora Mendelian mutations are present in sampled Hispanos and Lojanos

The Hispanos and Lojanos that were recruited were analyzed for the genomic mutations that have been characterized previously in these communities, notably in the *BRCA1*, *BLM* (Bloom syndrome), and *GHR* (growth hormone receptor) genes (Table 1S) (Ellis et al. 1998; Mullineaux et al. 2003; Rosenbloom and Guevara-Aguirre 2008). The *BRCA1* c.185delAG mutation was found to be present in 1 of the 33 Hispanos that were studied in the final genome-wide analyses, and in none of the Lojanos analyzed. The blm^{ash} mutation was found in two Hispano siblings and none of the Lojanos studied. Finally, 6 out of the 20 Lojanos analyzed carried homozygous mutations at the *GHR* c.E180 locus, 9 were heterozygous, and 5 were wild-type at this locus. None of the Hispanos carried this

mutation. These results confirmed that we were studying individuals from communities in which the presence of Diaspora mutations has been identified previously. It is important to note that we do not presume that these mutation frequencies reflect population-wide prevalences, as random, population-based recruitment was not performed.

Principal component analysis demonstrated continental admixture patterns similar to other Hispanic/Latino communities

Principal component analysis (PCA) was performed using the EIGENSOFT program to compare the Hispanos, Lojanos, and Mexicans to European, Native American, Jewish, and other global populations (Fig. 1a). The first two principal components of the global cohort demonstrated that Hispanos and Lojanos, like other continental populations with origins in Latin America, are the descendants of European and Native American groups with little contribution by sub-Saharan African populations to their genetic diversity (Bryc et al. 2010). By narrowing the number of populations studied to the Hispanos, Lojanos, Mexicans, European, Native American, and Jewish groups analyzed in previous studies (Altshuler et al. 2010; Atzmon et al. 2010; Bryc et al. 2010; Li et al. 2008), shows that on a genome-wide basis, Hispanos and Lojanos are separated by the first two components in PCA in a manner that demonstrated almost exclusively European and Native American, with very little apparent contribution from any Jewish population, including the Sephardim.

Population structure of sampled Hispanos and Lojanos demonstrated predominance of gender-biased admixture between Native Americans and non-African Old World founding populations

We applied the clustering algorithm, STRUCTURE, to investigate the genetic structure among Hispanos and Lojanos with a reference Mexican population and a world-wide panel of 895 individuals, to determine the number of ancestral clusters from which our study populations originated (Fig. 2). When examining $K = 3$ to $K = 6$, we observed the apparent European and Native American ancestry among Hispanos, Lojanos, and Mexicans, a low degree of Sub-Saharan African ancestry and a low degree of Middle Eastern ancestry that is more readily apparent in Jewish and Middle Eastern non-Jewish populations. The nature of this admixture was gender-biased. When examining patrilineal and matrilineal inheritance through analysis of mitochondrial and Y-chromosome haplotypes, two patterns were evident (Tables 1, 2). First, the Native American Y-chromosomal contribution was minimal in both Hispanos and Lojanos, largely represented by European (but in some cases possibly Near Eastern) haplogroups (Table 1). Second, the mitochondrial haplotypes among the Hispanos and Lojanos were almost exclusively Native American (Table 2). This suggests a two-way admixture model between European-derived populations and Native American ones in the formation of Hispano and Lojano communities, as in other continental populations far away from the Caribbean basin.

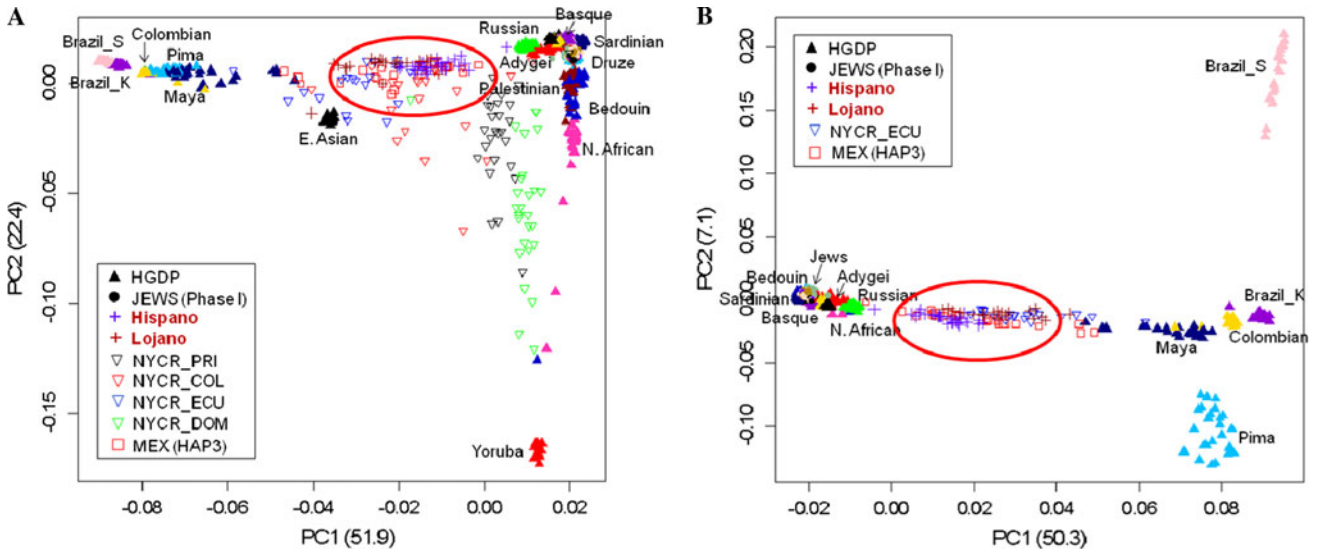

Fig. 1 PCA of unrelated Hispano and Lojano people (*circled*), within (**a**) global context; and (**b**) regional context (removing Central/Southern African and Eastern Asian populations). Other populations are MEX (Mexican), NYCP_DOM (Dominican), NYCP_PRI (Puerto Rican), NYCP_COL (Colombian), NYCP_ECU (Ecuadorian)

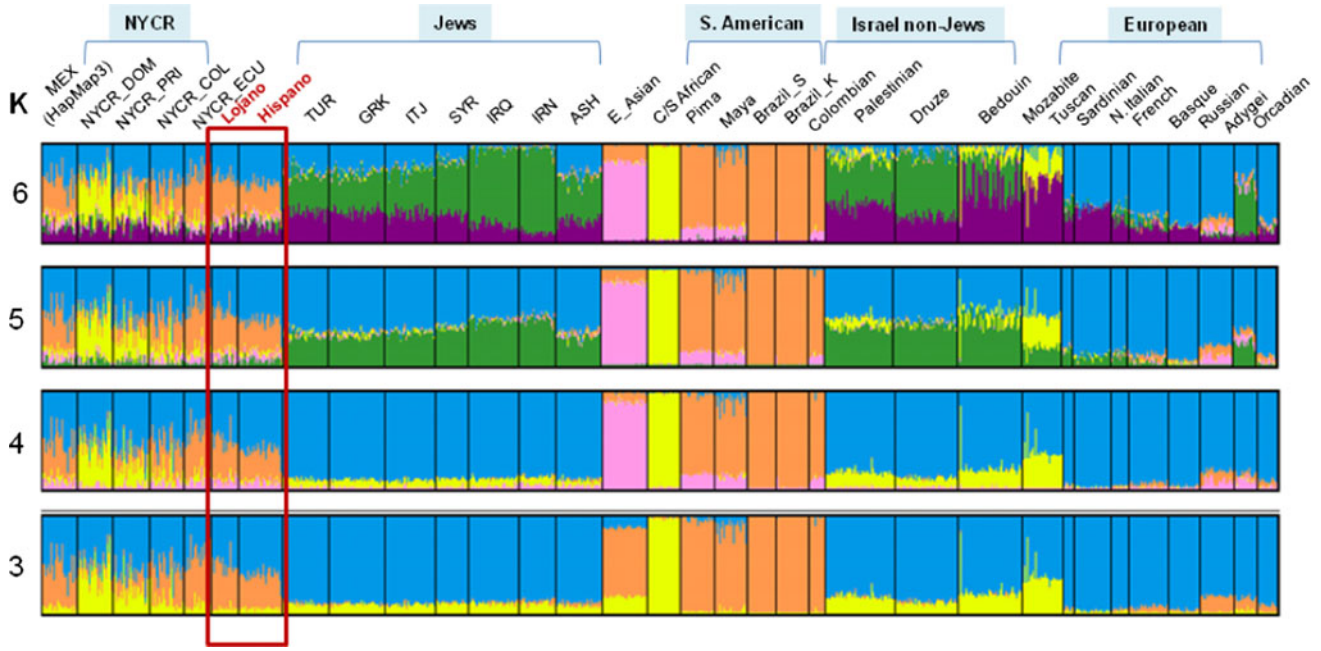

Fig. 2 STRUCTURE results ($K = 3$ to 6) for Hispano and Lojano populations, combined with selected HGDP worldwide populations. Each individual is represented by a *vertical line*, partitioned into *shaded segments* that correspond to membership coefficients in the subgroups. The analysis is based on 4,275 SNPs with potentially high informativeness for revealing population structure. The Lojano and Hispano populations are enclosed in a *bold box*

Identity-by-descent showed elevated cross-population sharing between Hispano, Lojano and Mexican samples

The frequency of identity-by-descent (IBD) between unrelated individuals in a population is indicative of effective population size (Wright 1931). We therefore analyzed the average genome-wide levels of IBD sharing within Latino ethnic groups. IBD sharing within Hispano and Lojano samples was higher than within other populations in this study, suggesting correspondingly higher levels of endogamy (Table 3).

We further analyzed rates of IBD sharing across different groups to investigate shared ancestry. Elevated cross-population sharing between Hispano, Lojano and Mexican samples (Table 4) was consistent with shared recent ancestry. When investigating potential shared ancestry between these groups and other populations, we observed that multiple populations shared segments IBD with Latinos (Table 4). More specifically, highest rates of such Latino-IBD sharing were observed in European and Tuscan samples followed by *Sephardic* and *Mizrahi* (Iranian, Iraqi and Syrian) Jewish communities. Lower rates of IBD were observed versus Ashkenazi samples in the Lojano samples, and to the Chinese group in Hispanos and Mexicans. Negligible IBD sharing with Yoruban samples was observed for all populations.

Ancestry deconvolution showed sharing compatible with a history of Latino admixture with Europeans, Native Americans and Sephardic Jews

Many Latino populations are well known to include genetic ancestry components from Native Americans, Europeans and Africans, all admixed within the last 20 generations. Hidden Markov Models are an accepted strategy to reconstruct the population origin of different segments along an admixed genome (Patterson et al. 2004). We employed such a method for ancestry deconvolution (Bonnen et al. 2010) to determine admixture proportions of the Hispano, Lojano and Mexican samples. Comparing potential European, *Sephardic* Jewish and Native American ancestry, we observed proportions compatible with a history of Latino admixture from these three ethnicities (Table 5). The Hispano samples showed increased European ancestry, whereas the Lojanos and Mexicans showed increased Native American ancestry.

We further considered the IBD-shared segments among Latino samples, to explore correlation between the occurrence of such segments and admixture source population. Interestingly, these segments across all examined Latino populations were substantially enriched for Native American ancestry. As such segments indicate a recent common ancestor of the samples who share them. This indicates a small number of recent Native American founders, relative

Table 1 The contribution of ancestral populations to Hispanos and Lojanos was marked by stark gender bias, as in other *Hispanic/Latino* communities: Y-chromosomal data

Sample	Gender	Y-Haplogroup	Likely origin	DYS													
				19	385-A	385-B	388	389-1	389-2	390	391	392	393	426	438	439	457
JHM0953	M	I-M253	Europe	14	13	14	14	11	27	22	10	11	13	11	10	11	16
JHM0954	M	I-M253	Europe	14	13	15	14	12	28	23	11	11	13	11	10	11	16
JHM0959	M	R-P312	Europe	14	11	14	12	13	29	23	11	13	13	12	12	11	15
JHM0961	M	R-P312	Europe	14	11	14	12	14	31	24	10	13	13	12	12	12	14
JHM0970	M	R-P312	Europe	15	11	14	12	13	30	24	10	13	13	12	12	12	14
JHM0971	M	R-P311 (xP312)	Europe	14	11	14	12	13	29	23	11	13	13	12	12	12	15
JHM0972	M	R-P312	Europe	14	11	13	12	13	28	24	10	13	13	12	13	12	15
JHM0974	M	R-P312	Europe	14	10	15	12	13	29	24	10	13	13	12	12	11	15
JHM0975	M	G-P15	Near East	15	14	14	13	12	27	23	10	11	14	11	10	11	16
JHM0976	M	R-P312	Europe	14	10	14	12	13	28	25	11	13	13	12	10	11	14
JHM0978	M	R-P25 (xM269)	Near East/ Jewish	16	13	15	12	14	29	22	11	13	13	11	11	12	14
JHM0982	M	R-P312	Europe	14	11	14	12	14	31	24	10	13	13	12	12	12	15
JHM0983	M	I-M253	Europe	14	13	15	14	12	28	23	11	11	13	11	9	11	16
JHM0985	M	R-P312	Europe	14	11	14	12	14	31	24	10	13	13	12	12	12	14
JHM1022	M	Q-M346 (xM3)	Americas	14	17	19	12	13	30	24	10	15	13	10	11	11	14
JHM1024	M	R-P312	Europe	14	11	15	12	13	30	24	11	13	13	12	12	11	15
JHM1025	M	J-M410 (xM67)	Near East	14	13	17	13	12	28	23	10	11	12	11	9	10	14
JHM1031	M	J-P58	Near East/ Jewish	14	13	15	16	13	30	23	10	11	12	11	10	11	14
JHM1035	M	I-M223	Europe	16	14	15	13	12	29	23	10	12	14	11	10	11	15
JHM1036	M	E-P1	Africa	15	17	17	12	13	30	21	12	11	13	11	11	11	14
JHM1037	M	R-P312	Europe	14	11	14	12	14	31	25	11	13	13	12	12	12	14

JHM 0950–JHM 0992 represent Hispanos and JHM 1022–JHM 1043 represent Lojanos

to other source populations. When considering IBD sharing in each Latino group separately, we further observed IBD sharing is also enriched for *Sephardic* ancestry ($p < 0.001$) within the Lojano community. The relative enrichments in *Sephardic* versus European ancestry in IBD-shared segments proved robust to the choice of a source population, showing similar results when compared to Yorubas, who likely did not contribute significantly in terms of ancestry (Table 2S).

Discussion

This work has important implications in terms of understanding the complex population structure that is the result of the founding of the various modern day New World populations. We hypothesized that we would be able to see traces of these colonial population dynamics of exclusion and integration of the Conversos into these two Latin American communities. Although they have not been previously subjected to the rigors of genome-wide analysis, there is a presence of founder mutations that are prevalent in Jewish communities. Two principal conclusions bear out. First, there is remarkable similarity between Hispanos and Lojanos and other communities with origins in Latin America in terms of the nature of admixture. Second, there are hallmarks of Jewish ancestry, with particular enrichment in the Lojano community. When performing PCA and clustering analyses on both groups, like other continental populations, both Hispanos and Lojanos appear to be descendants of Native American and European groups. There was marginal sub-Saharan ancestry in both of these communities, bolstered by low IBD as compared to Yorubans, which is unsurprising given the distance of the southwestern US and southern Ecuador from the principal slave trading routes in the Caribbean basin. In this two-way admixture model, it is clear that there was strong gender bias in the foundation of the Hispano and Lojano groups. Mitochondrial DNA was representative of Native American haplogroups, and Y-chromosomes non-Native American with representation from Old World populations.

Whereas the majority of Y-chromosomes analyzed from both groups were predictably of European origin, there was

Table 2 The contribution of ancestral populations to Hispanos and Lojanos was marked by stark gender bias, as in other *Hispanic/Latino* communities: mitochondrial DNA data

Sample	Gender	mtDNA HG	Likely origin	HVR1_motif
JHM0950	F	C	Americas	16223T,16295T,16298C,16325C,16327T
JHM0951	F	A	Americas	16111T,16223T,16239T,16290T,16319A,16362C,16497G,16512C
JHM0952	F	B	Americas	16092C,16111T,16183C,16189C,16217C,16299G,16483A,16519C
JHM0953	M	C	Americas	16223T,16298C,16325C,16327T
JHM0954	M	L3	Africa	16093C,16223T,16265T,16519C
JHM0955	F	B	Americas	16111T,16183C,16189C,16217C,16483A,16519C
JHM0956	F	B	Americas	16183C,16189C,16217C,16519C
JHM0958	F	A	Americas	16111T,16223T,16290T,16319A,16335G,16526A
JHM0959	M	A	Americas	16111T,16187T,16223T,16290T,16319A,16362C
JHM0960	F	A	Americas	16111T,16223T,16290T,16319A,16362C,16519C
JHM0961	M	B	Americas	16183C,16189C,16217C,16483A,16519C
JHM0962	F	B	Americas	16086C,16111T,16183C,16189C,16217C,16483A,16519C
JHM0966	F	B	Americas	16183C,16189C,16217C,16483A,16519C
JHM0967	F	C	Americas	16223T,16295T,16298C,16325C,16327T
JHM0968	F	B	Americas	16111T,16183C,16189C,16217C,16483A,16519C
JHM0969	F	A	Americas	16111T,16223T,16290T,16319A,16362C,16391A
JHM0970	M	A	Americas	16111T,16223T,16290T,16319A,16335G,16526A
JHM0971	M	A	Americas	16111T,16223T,16290T,16319A,16335G,16526A
JHM0972	M	B	Americas	16111T,16183C,16189C,16217C,16311C,16483A,16512C
JHM0973	F	B	Americas	16111T,16183C,16189C,16217C,16483A,16519C
JHM0974	M	A	Americas	16111T,16223T,16290T,16319A,16335G,16526A
JHM0975	M	B	Americas	16111T,16183C,16189C,16217C,16483A,16519C
JHM0976	M	B	Americas	16111T,16183C,16189C,16217C,16483A,16519C
JHM0977	F	D	Americas	16092C,16223T,16241G,16301T,16342C,16362C,16519C
JHM0978	M	B	Americas	16111T,16183C,16189C,16217C,16483A,16519C
JHM0980	F	B	Americas	16111T,16183C,16189C,16217C,16483A,16519C
JHM0981	F	A	Americas	16111T,16209C,16223T,16290T,16319A,16362C
JHM0982	M	H	Europe	16213A,16216G,16304C
JHM0983	M	A	Americas	16111T,16223T,16290T,16319A,16362C,16391A
JHM0985	M	A	Americas	16111T,16187T,16223T,16290T,16319A,16362C
JHM0986	F	B	Americas	16048A,16104T,16181G,16182C,16183C,16189C,16217C,16519C
JHM0988	F	A	Americas	16111T,16177G,16290T,16319A,16325C,16362C,16391A
JHM0990	F	B	Americas	16183C,16189C,16217C,16483A,16519C
JHM1022	M	B	Americas	16183C,16189C,16217C,16266T,16485A,16519C
JHM1023	F	D	Americas	16142T,16183G,16207G,16223T,16325C,16362C,16519C
JHM1024	M	B	Americas	16051G,16183C,16189C,16217C,16360T,16519C
JHM1025	M	C	Americas	16223T,16298C,16325C,16327T,16519C
JHM1026	F	B	Americas	16092C,16182C,16183C,16189C,16217C,16304C,16519C
JHM1027	F	B	Americas	16093C,16183C,16189C,16217C,16266T,16271C,16485A,16519C
JHM1028	F	U5	Europe	16129A,16192T,16270T,16304C,16311C
JHM1029	F	B	Americas	16183C,16189C,16217C,16266T,16271C,16485A,16519C
JHM1031	M	H	Europe	16183C,16189C,16519C,16527T
JHM1032	F	D	Americas	16142T,16183G,16207G,16223T,16325C,16362C,16519C
JHM1033	F	C	Americas	16180G,16223T,16298C,16325C,16327T
JHM1035	M	C	Americas	16180G,16223T,16298C,16325C,16327T
JHM1036	M	B	Americas	16183C,16189C,16217C,16296T,16311C,16519C
JHM1037	M	B	Americas	16092C,16182C,16183C,16189C,16217C,16241G,16289G,16519C
JHM1038	F	B	Americas	16092C,16183C,16189C,16217C,16241G,16289G,16519C

Table 2 continued

Sample	Gender	mtDNA HG	Likely origin	HVR1_motif
JHM1039	F	B	Americas	16183C,16189C,16217C,16290T,16381C,16519C
JHM1040	F	D	Americas	16051G,16172C,16209C,16223T,16256T,16291T,16325C,16362C
JHM1041	F	B	Americas	16092C,16182C,16183C,16189C,16217C,16304C,16519C
JHM1042	F	B	Americas	16183C,16189C,16217C,16258C,16266T
JHM1043	F	B	Americas	16183C,16189C,16217C,16240G,16362C,16519C

JHM 0950–JHM 0992 represent Hispanos and JHM 1022–JHM 1043 represent Lojanos

Table 3 Evidence for recent genetic relatedness based on IBD sharing: IBD sharing within groups

ASH	IRN	IRQ	SYR	ITJ	GRK	TUR	HSP	LOJ	MEX	TSI	CEU	CHB	YRI
77.0	170.0	152.2	89.8	130.6	50.2	42.2	113.3	131.0	71.3	49.6	59.9	75.2	8.9

The high levels of endogamy within Hispano, Lojano and Jewish populations are reflected by the high levels of IBD sharing. The populations are Ashkenazi Jewish (ASH), Iranian Jewish (IRN), Iraqi Jewish (IRQ), Syrian Jewish (SYR), Italian Jewish (ITJ), Greek Jewish (GRK), Turkish Jewish (TUR), Hispano (HSP), Lojano (LOJ), MEX (Mexican), TSI (Tuscan), CEU (CEPH Europeans), Chinese from Beijing (CHB), Yoruba (YOR) from Ibadan, Nigeria (YRI). The high levels of endogamy within Hispano, Lojano and Jewish populations are reflected by the high levels of IBD sharing

Table 4 Evidence for recent genetic relatedness based on IBD sharing: total average IBD sharing across populations (cM per pair of individuals)

	ASH	IRN	IRQ	SYR	ITJ	GRK	TUR	HSP	LOJ	MEX	TSI	CEU	CHB
IRN	11.92												
IRQ	16.02	31.73											
SYR	17.96	15.43	31.59										
ITJ	24.51	15.20	24.59	25.74									
GRK	21.35	15.05	24.99	27.00	33.68								
TUR	22.93	15.61	26.24	28.72	33.55	33.69							
HSP	12.16	10.16	17.41	16.69	18.81	18.96	19.87						
LOJ	8.36	7.73	12.41	11.62	13.01	12.74	13.57	43.75					
MEX	10.34	9.25	14.80	14.74	15.95	15.95	17.15	52.07	53.69				
TSI	19.08	17.57	28.17	27.22	30.15	30.13	31.10	26.37	17.80	22.71			
CEU	19.69	16.37	25.97	25.42	29.45	29.28	30.83	30.05	20.55	25.75	45.31		
CHB	1.88	1.87	3.18	2.42	2.52	2.65	2.69	10.43	10.03	12.15	3.56	3.88	
YRI	0.01	0.01	0.03	0.02	0.03	0.02	0.02	0.05	0.02	0.08	0.03	0.02	0.02

The Hispano and Lojano groups exhibit the highest cross-population sharing, with Sephardic (Greek, Turkish, Italian) Jews as their most closely related Jewish group

a minority that appeared to be derived from Middle Eastern origin, with a strong likelihood of cryptic Jewish or other Middle Eastern origin. That historically Christian and Spanish-speaking populations likely have cryptic Jewish or Middle Eastern ancestry has been demonstrated by analysis of paternal lineages throughout the Iberian Peninsula (Adams et al. 2008), and in genome-wide surveys of admixture in various Caribbean and continental Latin American populations (Bryc et al. 2010). The Hispanos and Lojanos are known to harbor mutations that are prevalent within Jewish Diaspora communities, providing further evidence for possible Jewish origins (Mullineaux et al. 2003; Rosenbloom and Guevara-Aguirre 2008). In addition, the Bloom syndrome, blm^{Ash} mutation, originally identified in Ashkenazi Jews, was found in the Hispano cohort and in Hispanic/Latino individuals living in territories once part of the Spanish Empire, including the Southwestern US, Mexico, and El Salvador (Ellis et al. 1998).

The conclusions drawn from this work are inevitably informed by the history of Jews before and after their migration to the New World. Jews who would become known as Sephardim lived in the Iberian Peninsula as far back as the days of the Roman Empire. During the

Table 5 Ancestry deconvolution for the regions shared IBD across Mexican, Hispano and Lojano populations with respect to European (EU), Sephardic (SEPH) and Native American (NA) origin

	MEAN	MEX	HSP	LOJ
EU				
MEX	0.309	0.206	0.239	0.205
HSP	0.362	0.276	0.344	0.265
LOJ	0.312	0.22	0.239	0.291
SEPH				
MEX	0.297	0.177	0.205	0.171
HSP	0.342	0.226	0.327	0.211
LOJ	*0.305*	0.203	0.232	**0.342**
NA				
MEX	*0.394*	**0.617**	**0.557**	**0.624**
HSP	*0.296*	**0.498**	**0.328**	**0.524**
LOJ	*0.382*	**0.576**	**0.53**	0.367

The reported "mean" represents the estimated average genome-wide ancestry for all individuals within a population. Other entries in the table represent the estimated fraction of ancestry in correspondence of IBD segments (see "Materials and methods" for details). For all pairs of populations recent IBD sharing was enriched for Native American origin, with the exception of the sharing within Lojano samples for which recent sharing was enriched for Sephardic Jewish origin. The enrichment is italicized for the genome-wide value versus bold for IBD sharing

Inquisition, many Jews fled Iberia, resulting in the Sephardic Diaspora that settled in the territories of the Ottoman Empire. Others chose to remain for the meantime in the peninsula by fleeing into Portugal. Before the edicts of conversion and expulsion, the Jewish portion of the Portuguese population was estimated to be 3–5% of the total population (Prinz 1973; Rowland 2001). It is estimated that approximately 100,000 Jews fled into Portugal, resulting in a conservative estimate of doubling Portugal's overtly practicing Jewry (Ordóñez-Chiriboga 2005; Rowland 2001). As Portugal became integrated into the Spanish crown under Felipe II, the degree of Portuguese Converso migration led authorities in the New World to use the terms, "Portuguese," "Jew," and "Converso" interchangeably (Ordóñez-Chiriboga 2005). Those migrants who wished to maintain their ancestors' religion while continuing to demonstrate a veneer of Catholicism would be able to do so under less scrutiny in these New World territories, especially the fringes of northern New Spain in modern day Colorado and in the mountainous regions of colonial Peru in what is now Ecuador (Alberro 2001).

In contrast, many Converso migrants who had converted wished to offer their children escape from the constant suspicion of the metropolitan territories of the Peninsula: these people chose to integrate versus be excluded (Alberro 2001). That the Conversos joined their "Old Christian" brethren and migrated in significant numbers to the Americas is not in doubt. Conversos sailed with Columbus, helped topple the indigenous Aztec and Incan Empires, and were integral members of the political and religious hierarchies of the Viceroyalties of New Spain and Peru (Alberro 2001; Ordóñez-Chiriboga 2005; Rowland 2001; Uchmany 2001). It has been difficult to ascertain the degree of intermarriage in the New World between newly converted Christians and those Christians from older communities. In contrast, the historical record in the Old World suggests that there was a significant degree of intermarriage between both groups, generation after generation; one would presume that such a trend would have held out in the colonial outposts of Old World Iberian society.

Comparing the Hispanos and Lojanos to the Greek and Turkish Jewry was necessary given the history of the *Sephardic* Diaspora to the Ottoman Empire at the turn of the 16th century, now the modern day republics of Greece and Turkey. When studying the *Sephardic* Jewry descended from residents of Salonica and Istanbul, it was found that degrees of admixture between Near Eastern and European ancestors in Sephardim to be on the order of 30–60% (Atzmon et al. 2010), likely reflecting the more ancient admixture with local European populations in the Jewish communities of the Iberian Peninsula prior to 1492. However, when performing PCA, the Sephardim, like other Jewish populations, were found to cluster independently within a larger Jewish cluster in comparison to putative reference populations from the Near East and Europe (Atzmon et al. 2010). In this study, IBD analysis demonstrated the greatest similarity between Hispanos and Lojanos and European populations, followed by *Sephardic* populations. There was a greater proximity and sharing between Lojanos and Sephardim compared to Hispanos and Mexicans. Hispanos and Mexicans, in contrast, had a greater degree of similarity with Native American populations. When trying to study the contribution of Sephardim (already an admixed group) to the admixture of Europeans with Native Americans to produce the modern Hispano and Lojano communities via ancestry deconvolution, similar trends emerged.

This allows us to draw several conclusions about our Hispano and Lojano cohorts. First, there is observable Sephardic ancestry in both Hispanos and Lojanos, providing genomic credence to the historical narrative of the *Frontier Phenomenon* of Converso migration to the New World. Second, Lojanos likely have a greater degree of Converso ancestry than Hispanos. Third, the maintenance of mutations previously characterized in the Jewish Diaspora communities in populations with non-Jewish ancestry can be due to the endogamy noted during genome-wide analysis. Without attaching any religious or social

implications to this data, it becomes evident that Hispanos, Lojanos, and likely, many Latin Americans have a certain degree of cryptic Jewish ancestry. Such cryptic ancestry needs to be accounted for in future genome-wide studies, especially those association studies that seek to correlate heritable risk to disease.

Materials and methods

Study participants

Participants were recruited from communities previously demonstrated to have a measurable prevalence of the BRCA1 c.185delAG (Hispano) and GHR c.E180 mutations (Lojano), two mutations that are common within Jewish communities (Ostrer 2001). Hispanos were recruited by newspaper advertisement and word of mouth in the Culebra, Colorado, in compliance with Institutional Research Board-approved research protocols both in the United States and in Ecuador. These included 71 individuals who all indicated that their families had been long-term residents in the San Luis Valley. Some of the participants were known to be directly related to one another. All were included in the direct mutation analysis. Only 33 individuals who were selected on the basis of not being related by IBD to one another were included in the microarray and Y-chromosomal and mitochondrial analyses. Lojanos were recruited in Loja, Ecuador. These included 50 individuals either affected with Laron syndrome or their parents or siblings. All were included in the direct mutation analysis. Only 20 individuals who were selected on the basis of not being related by IBD to one another were included in the microarray and Y chromosomal and mitochondrial analyses.

Datasets

We genotyped the Hispano and Lojano samples from Colorado in US and the Loja province of Ecuador, respectively, on Affymetrix Human SNP 6.0 arrays, with call rates >99% and no gender mismatch. The samples were also tested for relatedness using genome-wide IBD estimates. This dataset were further combined with (1) 237 samples from the Jewish HapMap Project (Affymetrix 6.0), including Iranian, Iraqi, Syrian, Italian, Turkish, Greek and Ashkenazi Jews (Atzmon et al. 2010); (2) 4 US Hispanic/Latino populations (27 Dominicans, 26 Colombians, and 20 Ecuadorians, as well as 27 Puerto Ricans) from Illumina 610 K arrays (Bryc et al. 2010); (3) 50 US Mexican samples from HapMap3 (Affymetrix 6.0) (Altshuler et al. 2010); and (4) 508 selected samples from the Human Genome Diversity Panel (HGDP) on Illumina 650 K platform, including North African (Mozabite), Native American (Brazil_Karitiana, Brazil_Surui, Colombians, Mexican_Maya, Mexican_Piman), Middle Eastern non-Jews (Bedouin, Druze, and Palestinian), and Europeans (Orcadian, Adygei, Russian, Basque, French, Bergamo, Tuscan, and Sardinian) (Li et al. 2008). We used annotation information to determine the strand to make sure the SNPs from different datasets are on the same strand, and then merged data from the various platforms using the PLINK, version 1.04 (Purcell et al. 2007). The final dataset contains genotypes of 148,724 SNPs across 895 individuals. To accommodate the need for a larger set of cross-platform markers, samples from the HGDP data set were not included for IBD analysis, as detailed in the specific section.

Mutation analysis

GHR and BRCA1

Standard Applied Biosystems (ABI) two-step TaqMan allelic discrimination (AD) PCR cycling conditions were employed for both GHR and BRCA1: 95°C/10 min, [95°C(1 min)/60°C(1 min)] × 40 cycles. The assays were run using a 2X ABI Genoytping Master Mix (Applied Biosystems, Foster City, CA, part#4371355) and run on an Applied Biosystems 7900HT.

GHR

A TaqMan AD assay (108 bp amplicon) was designed to genotype the p.E180 (GAA-TAA) mutation (Fang et al. 2008): (a) GHR-F primer: CAGATATTCAGAAAGGATG GATGGT; (b) GHR-R primer: AGTCAAAGTGTAAGGT GTAGCAACATCTTA; (c) GHR wild type TaqMan probe: VIC-TTCAATACAAAGA[A]GTAAATG-MGBN FQ; (d) GHR mutant TaqMan probe: FAM-CAATACAA AGA[G]GTAAATG-MGBNFQ.

BRCA1

A TaqMan AD assay (101 bp amplicon) was designed to genotype the g.185delAG mutation (Simard et al. 1994): (a) BRCA1_dAG-F primer: TCGCGTTGAAGAAGTACA AAATGT; (b) BRCA1_dAG –R primer: TAGGAATCCC AAATTAATACACTCTTGTl (c) BRCA1_dAG wild type TaqMan probe: VIC-AAAATCTT[AG]AGTGTCCCATC T-MGBNFQ; (d) BRCA1_dAG mutant TaqMan probe: FAM-AGAAAATCTT[*]AGTGTCCCATCT-MGBNFQ.

BLM

Genotyping for the c.2207_2212delinsTAGATTC mutation in exon 10 of the BLM gene (blm^{Ash}) was performed

by allele-specific oligonucleotide hybridization of the blotted 305 bp amplicon as previously described (Oddoux et al. 1999).

Population structure and relationships

PCA

For principal component analysis, we used *Smartpca* program from EIGENSOFT package (version 2.0) (Patterson et al. 2006). The analyses were run without the removal of outliers.

STRUCTURE

To infer the population structure, we used a Bayesian model-based clustering method, implemented in the *STRUCTURE* software package (Pritchard et al. 2000). To reduce the running time while still maintaining the information of population structure within the dataset, we used 4,275 SNPs with the highest informativeness contained. The informativeness of SNPs was estimated using average genetic distance difference (δ) among populations studied. For each population pair, δ is calculated as the sum of the absolute differences between allele frequencies. Markers were then ranked and top 5% of SNPs (with interval >200 kb) were selected for *STRUCTURE* analysis. The program was run 5 times for K values 3–6. All structure runs used 10,000 burn-in cycles followed by 10,000 MCMC iterations, assuming correlated allele frequencies and admixture model with separate alpha estimated for each population. The results from all replicates for each K were aligned with *CLUMPP* (Jakobsson and Rosenberg 2007) and mean individual Q matrix was plotted using DISTRUCT (Rosenberg 2004).

IBD analysis

Phasing

We phased the genotype data for each group using the Beagle software package (Browning and Browning 2007), then detected IBD segments using GERMLINE (Gusev et al. 2009) in Genotype Extension mode. GERMLINE identifies short phased perfect matches across pairs of individuals, which are then extended to identify long IBD segments with a probabilistic approach. The identified segments were used to exclude close relatives from the analysis, obtain statistics on the average total IBD sharing within and across groups and identify cross-population regions of increased sharing.

GERMLINE IBD detection

The GERMLINE software package can be used in Haplotype Extension (in cases where the data is reliably phased) or Genotype Extension, which can be used on poorly phased data. In the Genotype Extension mode only mutually homozygous markers are considered and a segment is extended until a specified number of mismatching sites is encountered. We performed IBD detection using Genotype Extension with parameters "-min_m 3 –bits 64 –err_het 1 –err_hom 0". The analysis was run for unrelated samples from the following groups: Yoruban ($N = 113$), Mexican ($N = 47$), Tuscan ($N = 88$) and Western European ($N = 104$) samples from the HapMap 3 data set; Ashkenazi ($N = 34$), Iranian ($N = 28$), Iraqi ($N = 37$), Syrian ($N = 25$), Italian ($N = 37$), Greek ($N = 42$), Turkish ($N = 34$) from the Jewish HapMap data set; Hispano ($N = 33$) and Lojano ($N = 20$) samples. HGDP samples were not included to obtain a larger intersection for the cross-platform markers. After phasing, a total of 622,090 SNPs were available for the analysis.

Filtering of cryptic relatives

All samples were initially scanned for cryptic relatedness. Following IBD detection we identified pairs of individuals for which IBD sharing suggested unreported close ancestral relationships and excluded some samples from further analysis. Specifically we excluded individuals in relationships for which the genome-wide sharing was at least 800 cM and at least ten segments of length ≥10 cM could be identified.

Average Total IBD sharing

The total sharing between an average pair of individuals from two different populations was computed summing the length (in CMs) of all IBD segments detected across the two populations and normalizing by the number of possible pairs of individuals (the product of the cardinality for the two groups). We normalized by $\binom{N}{2}$ possible pairs when computing the average total sharing within a population of sample size N.

Regions of increased sharing

We analyzed the genome-wide physical distribution of IBD sharing and identified loci for which the sharing is higher across specific groups (Table 2S). The physical distribution of the sharing between two populations at a particular locus is obtained by the sum of IBD segments overlapping the locus normalized by the total number of potential pairs of individuals for the two populations (the product of their cardinality). To control for regions which are commonly

enriched for IBD sharing and artifacts due to noise in the IBD discovery phase, we normalized the sharing density by the density obtained across all the analyzed populations. We reported regions for which the normalized density is higher than the mean plus four times the standard deviation (Table 3S). To obtain robust sharing distributions for this analysis the populations were grouped as follows: *Mizrahi* (Iraqi, Iranian and Syrian individuals); *Sephardic* (Italian, Greek and Turkish individuals); Hispano/Lojano; Mexican; Ashkenazi. We separately performed a more detailed analysis using Mexican, Hispano and Lojano samples with no additional grouping.

Ancestry deconvolution

We used the Xplorigin software package (Bonnen et al. 2010) to investigate the proportion of European, Native American and Jewish ancestry of Hispano and Lojano samples in comparison to another Hispanic/Latino cohort from Mexico. Xplorigin builds a database of short haplotype frequencies for three reference populations, which are assumed to be the source of admixture for a studied group of samples. The haplotype frequencies are probabilistically used to assign locus-specific ancestry proportions to the analyzed individuals. Ancestry deconvolution was also applied to investigate the remote origin of regions shared IBD across populations.

Xplorigin analysis

We trained the Xplorigin software using 98 randomly selected phased haplotypes from the following groups: European Basque and French from the HGDP dataset; Sephardic Italian, Greek and Turkish from the Jewish HapMap dataset; Native American Pima, Surui and Maya samples from the HGDP dataset. After pruning some markers during computational phasing, the number of makers used for this cross-platform analysis was 150,157SNPs. For each of the three reference groups we determined LD blocks and the frequency of haplotypes and transitions between haplotypes using Haploview (Barrett et al. 2005). The genome was then partitioned into short haplotype blocks, and Xplorigin's hidden Markov model was used to assign the most likely proportion of ancestry from the three reference populations to each observed individual.

Xplorigin analysis of IBD segments

We analyzed the proportions of ancestry in correspondence of IBD segments within and across populations. To overcome phase uncertainty for an IBD segment shared by two individuals, we considered the ancestry of both maternal and paternal chromosomes reported by Xplorigin in correspondence of the IBD region. The values reported in Table 5 were computed as follows: given a number of IBD segments between individuals of two populations P1 and P2, we report the average proportion of IBD ancestry of individuals from P1 in position P1-P2 of the table, and the average proportion of IBD ancestry of individuals from P2 in position P2-P1. The ancestry of IBD sharing within a population (table entries in positions P1-P1) was computed for both individuals of an IBD sharing pair. The reported mean ancestry proportion is computed as the genome-wide average ancestry proportion. To test for significance of the differences between genome-wide ancestry proportion and IBD ancestry proportions we performed random permutations of the IBD segments. We randomly shuffled IBD segments between populations P1 and P2, testing the ancestry proportions for the permuted set of IBD segments. The deviation from the genome-wide averages in correspondence of IBD segments was never observed for 1,000 random permutations of each table entry.

mtDNA and Y-chromosome mapping

Y-chromosomal haplotypes were assigned by analysis of the genotypes of the following 14 short tandem repeats (STRs): DYS19, DYS385-A, DYS385-B, DYS388, DYS389-1, DYS389-2, DYS390, DYS391, DYS392, DYS393, DYS426, DYS438, DYS439, and DYS457 (Redd et al. 2002). A hierarchical genotyping strategy was used in which major haplogroups were predicted based on the array of Y-STR alleles contained on each Y-chromosome, and then confirmed genotyping of a smaller set of SNPs as described previously (Karafet et al. 2010). Sequences of HVS-1 of the mtDNA control region were determined from position 16000–16540. mtDNA haplogroups were confirmed with RFLP (restriction fragment length polymorphism) typing of coding-region sites (Behar et al. 2004). For the purpose of present study, we genotyped the markers that define the main (A, B, C, D) and minor (X) founder haplogroups in Native Americans, the major (L0, L1, L2) and a minor L3 African haplogroups, and additional markers present in Caucasians (N1, J, K, HV, H, V, T, U, W). All samples have also been typed for SNPs defining M, N, and R branches to exclude possible recurrent mutations.

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