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The E180splice Mutation in the *GHR* Gene Causing Laron Syndrome: Witness of a Sephardic Jewish Exodus from the Iberian Peninsula to the New World?

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Laron syndrome (LS) is a genetic disorder caused by mutations in the growth hormone receptor (*GHR*) gene. The most frequent *GHR* mutation is E180splice (rs121909360), which was initially found in an inbred population of Spanish descent in Ecuador and subsequently in Israel, Brazil, Chile, and the United States. The aim of the present study is to determine if the E180splice mutation arose from a common origin. We studied 22 patients with LS from Ecuador, Israel (of Moroccan origin), Brazil, Chile, and the United States (of Mexican origin) who were homozygous for the E180splice mutation and compared them to control individuals for markers surrounding the *GHR*, intragenic polymorphisms, and Y-chromosome STR. An identical haplotype was found in all but one of the subjects carrying the E180splice mutation: D5S665: 150/150; D5S2082: 192/192; D5S2087: 246/246; rs6179 G/G; and rs6180 C/C. One patient differed from the others only at D5S2082 (168/192). This haplotype is rare (~1%) in control individuals and confirmed that the E180splice-associated haplotype was not derived from independent origins but represented recombination from a common ancestor. The analysis of paternal lineage markers showed that 50% belong to haplogroup R1b (found in Portugal and Spain) and 40% to haplogroups J and E (typical in the Middle East and in Eastern European Jews). The germline *E180Splice* mutation appears to have originated from a single common ancestor. The presence of Y-chromosome markers associated with Sephardic populations

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in persons harboring the E180splice mutation provides genetic evidence in support of the historical tracking of the exodus of this specific population. © 2014 Wiley Periodicals, Inc.

Key words: growth hormone receptor deficiency; growth hormone insensitivity; Laron syndrome; growth hormone receptor; mitochondrial haplogroups; Y-chromosome haplogroups; lineage markers

INTRODUCTION

The most common genetic cause of Laron syndrome (LS) or GH insensitivity (GHI), (LS, OMIM #262500) are mutations or deletions in the GH receptor (*GHR*, OMIM *600946) gene resulting in GHR deficiency [Laron, 2004; Shevah and Laron, 2011]. Affected individuals manifest severe postnatal growth impairment and other clinical features [Laron, 2004; Rosenbloom et al., 1999]. Of the more than 70 different mutations in the *GHR* that have been demonstrated [David et al., 2011], the E180splice mutation is the most prevalent. This single nucleotide exchange (c.594A>G, rs121909360) in exon 6 does not change the amino acid encoded by codon 198 (or 180 in mature peptide), but activates a cryptic 5′donor splice site that results in an in-frame deletion of eight residues (p.V199_M208 del) within the GHR extracellular domain and impedes receptor trafficking to the cellular membrane [Fang et al., 2008]. The E180splice mutation was first described in persons of Spanish descent from Southern Ecuador. This population of ~100 individuals is the largest population of individuals with LS/GHI due to GH receptor defects described to date [Berg et al., 1992; Guevara-Aguirre et al., 2011]. The first non-Ecuadorean individual carrying this mutation was a Jewish patient from Israel of Moroccan origin [Berg et al., 1994]. This homozygous mutation was also noted in several Brazilian subjects from different families [Jorge et al., 2005] and in two sibs with LS/GHI from southern Chile [Espinosa et al., 2008]. A common origin of the E180splice mutation has been postulated [Berg et al., 1994; Jorge et al., 2005; Espinosa et al., 2008; Rosenbloom and Guevara-Aguirre, 2008], a hypothesis supported by the presence of the most common intron 9 haplotype [Amselem et al., 1989] in all investigated patients [Berg et al., 1994; Jorge et al., 2005; Espinosa et al., 2008]. In the present study, we expanded on these earlier observations and by analyzing polymorphic markers surrounding the *GHR* and the Y-chromosome haplotypes in several affected subjects from different geographic areas, provide evidence for a founder effect for the E180splice mutation.

SUBJECTS AND METHODS

Patients

The study was approved by the Ethics Committee of each institution and informed written consent was obtained from all patients. Genomic DNA was available from 22 individuals (10 males) homozygous for *GHR* E180splice mutation (6 Ecuadorian, 1 Israeli of Moroccan origin, 12 Brazilian, 1 Chilean, and 2 Americans of Mexican origin), 13 first-degree relatives heterozygous for the E180splice mutation (seven males) from five distinct families and from 42 normal individuals (30 from Brazil and 12 from Israel) and five patients with LS/GHI (three from Israel and two from Brazil) caused by *GHR* mutations other than the E180splice.

Microsatellites Analysis

Three highly informative polymorphic markers in the short arm of chromosome 5 and localized around the *GHR* gene (reference sequence NM_000163.4) were amplified by polymerase chain reaction (PCR): D5S665 [0.38 centimorgan (cM) from *GHR*], D5S2082 (0.69 cM) and D5S2087 (1.52 cM). The oligonucleotide primers were labeled with fluorescent dye. The amplified fragments of microsatellite were submitted to a capillary electrophoresis in the ABI PRISM 3130 sequencer and were analyzed by the GeneScan® software, both from Applied Biosystems (Foster City, CA). Additionally, several intragenic single-nucleotide polymorphisms (SNP) (rs6179, rs6180, IVS9 haplotype) and the presence or absence of GHR exon 3 were genotyped as previously described [Amselem et al., 1989; Jorge et al., 2005].

Y-Chromosome Haplotype Analysis

The set of 17 Y-STRs was amplified from six unrelated male LS/GHI patients and three first-degree male relatives from three unrelated female subjects with LS/GHI, using the AmpFlSTR® YfilerTM kit (Applied Biosystems) which contains the markers DYS19, DYS389 I, DYS389 II, DYS390, DYS391, DYS392, DYS393, DYS385 a/b, DYS438, DYS439, DYS437, DYS448, DYS456, DYS458, DYS635, and Y GATA H4. Capillary electrophoresis was done in an ABI PRISM 3130 sequencer, and sizes were assigned to the different fragments using GeneMapper® software. The nomenclature of alleles followed the recommendations of the DNA Commission of the International Society of Forensic Genetics, except for locus Y GATA H4, which was named on the basis of the allelic ladder supplied with the AmpFlSTR® YfilerTM kit. The classification of Y-chromosome haplogroup for each male participant genotyped was done using haplogroup prediction program FTDNA 2.0 (http://www.hprg.com/hapest5/index.html).

Mitochondrial Haplotype Analysis

DNA samples from 17 patients were amplified by a single PCR to analyze the entire sub-regions HV1, HV2, and HV3 of mtDNA control region, using *primers* L15879 and H727. PCR products were purified using EXO/SAP, and sequencing was done using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems) according to manufacturer's protocol. Capillary electrophoresis was performed using the ABI PRISM 3130 sequencer and resultant sequences analyzed using specific software BioEdit (http://www.mbio.ncsu.edu/BioEdit/BioEdit.html). The sequences obtained were compared with the Cambridge Reference Sequence (rCRS) [Andrews et al., 1999].

RESULTS

Microsatellite Analysis

Nine different alleles were identified for the D5S2087 marker, ranging from 146 to 248 bp. For the D5S665 and D5S2082 markers, seven alleles were identified, ranging from 142 to 154 and 182 to 200 bp, respectively. The alleles 146 bp for D5S665, 194 bp for D5S2082 and 246 bp for D5S2087 were the most frequent alleles in Brazilian and Israeli control individuals, with an allele frequency of 38%, 55%, and 32%, respectively.

An identical haplotype was identified in all but one of the apparently unrelated patients carrying the E180splice mutation: D5S665: 150/150; D5S2082: 192/192; D5S2087: 246/246; rs6179 G/G rs6180 C/C, IVS9 haplotype-I and GHRfl. One Ecuadorian patient was heterozygous for D5S2082 168/192 bp. This haplotype segregated perfectly in available parents and was not found in LS/GHI patients harboring other mutations or in the control group. The microsatellite frequencies of controls indicated that the 150-192-246 haplotype is relatively rare (~1%). Based on this result, it is unlikely that the E180splice, associated with the 150-192-246 haplotype and present in all families, was derived from independent origins ($P < 10^{-10}$). The alternative hypothesis is that individuals harboring the mutation share a common ancestor, from whom they inherited the 150-192-246 haplotype.

Y-Chromosome Haplotype Analysis

To verify the hypothesis that the individuals with E180splice mutation share a common ancestor, we analyzed the paternal lineage origin studying Y-STRs of 10 families (Table I). Five out of 10 showed the same haplogroup R1b, which is predominantly found in Western Europe (Spain and Portugal), one of them showed the haplogroup J, and three participants had haplotypes which belonged to haplogroup E (two participants showed sub haplogroup E1b1a and one had E1b1b). The haplogroups J and E are typically found in the Middle East and in Eastern European Jews. One subject from Ecuador had an Amerindian haplotype (haplogroup Q) (Table I).

Mitochondrial Haplotype Analysis

To verify the maternal lineage origin we analyzed the mtDNA control region polymorphisms of 11 Brazilian, one Israeli, and five Ecuadorian subjects, and 11 first-degree relatives (Table I). Two Brazilian and all five Ecuadorian subjects carry the Amerindian haplogroup B (with different subhaplogroups, B4b, B2, B4). Three Brazilian individuals have the European haplogroup J (subhaplogroup J2b), typical of those from the Balkan Peninsula. The other six Brazilian subjects carry the African subhaplogroup L2b that originated in West African, haplogroup L3b that originated in sub-Sahara Africa and migrated to the Mediterranean coast, and subhaplogroup L1c1a1 that came from Central Africa. The Israeli patient showed subhaplogroup R0, which occurs frequently in Arabia.

DISCUSSION

Since the initial description of *GHR E180splice* as the most common mutation in patients with severe GHI/LS [Berg et al., 1992, 1994], it was hypothesized that this mutation had a common origin. This mutation was identified in countries that were colonies of Spain [Berg et al., 1992; Espinosa et al., 2008] and Portugal [Jorge et al., 2005]. Interestingly, it was not described in GHI patients from the Iberian Peninsula, but was identified in a Jewish Israeli patient of Moroccan origin [Berg et al., 1994]. Based on the history

TABLE I. Summary of Results From Y-Chromosome and Mitochondrial DNA Haplogroups

Family ID	Country	Number of individuals	Y-chromosome haplotype	Geographic origin	Mitochondrial haplotype	Geographic origin
1	Israeli	1	[a]		R0	Arabian Peninsula
2	Brazil	1	[a]		B4b	Amerindian
3	Brazil	3	R1b	Western Europe	L2b/L3b	West Africa
4	Brazil	6	R1b	Western Europe	J2b	Balkan Peninsula
5	Brazil	2	R1b	Western Europe	L2b	West Africa
6	Brazil	3	E1b1a	Sub Saharan Africa	B2/J2b	Amerindian/Balkan Peninsula
7	Brazil	1	NA		J2b	Balkan Peninsula
8	Brazil	2	E1b1b	Mediterranean	L3b	West Africa
9	Brazil	4	J1	Arabian Peninsula	L1c1a2/A2	Central Africa/Amerindian
10	Ecuador	1	[a]		B4b	Amerindian
11	Ecuador	1	[a]		B2	Amerindian
12	Ecuador	1	Q	Amerindian	B4	Amerindian
13	Ecuador	1	[a]		B4b	Amerindian
14	Ecuador	1	E1b1a	Sub Saharan Africa	B4	Amerindian
15	Chile	3	R1b	Western Europe	NA	
16	United States	1	R1b	Western Europe	NA	
17	United States	1	[a]		NA	

NA, not available.
[a]Female.

of the Iberian Peninsula, the proposed explanation for this finding was that the *E180splice* mutation had originated in the Mediterranean or Middle Eastern region and was carried to South America by early settlers of Iberian Jewish descent known as Sephardim [Berg et al., 1994] (Fig. 1).

Historically, the Sephardi Jews lived in the Iberian Peninsula as far back as the times of the Roman Empire. During the Inquisition, around 1492, many Spanish Jews fled Iberia, resulting in the Sephardic Diaspora. Some settled in Portugal, others in North Africa and many converted to Christianity [Prinz, 1973; Rowland, 2001]. Several of these "new Christians" (or Conversos) emigrated from the Iberian Peninsula to the New World [Rowland, 2001; Chiriboga, 2005]. The first register of "new Christians" in the northeast region of Brazil dates from 1542. At the end of the XVI century they constituted around 14% of the population of that region. Additionally, it is estimated that one-third of early Spanish immigrants were Conversos [Chiriboga, 2005; Velez et al., 2012].

It is well known that in Iberian Peninsula, besides the Sephardi Jews, also occurred a wave migration from North Africa in 711 CE crossed from Marocco, considered and showed by Y-STR haplotypes study being more recent and with minor admixture contribution of patrilineal ancestry [Adams et al., 2008]. Under this point of view, we cannot ignore the possibility of this mutation has been originated in this population (Spanish Muslims converted to Christianity or Moriscos), although there is no report of patients with this Islamic origin and the *E180splice* mutation.

The presence of the most common haplotype, defined by six SNPs located in the intron 9 of the *GHR* gene, found in all patients harboring the *E180splice* suggests a common origin for this mutation [Berg et al., 1992, 1994; Jorge et al., 2005; Espinosa et al., 2008]. Our analysis of polymorphic markers surrounding *GHR* definitively establishes that patients carrying *E180splice* mutation have a common ancestor. The analysis of chromosome Y, furthermore, supports the Sephardic origin of this mutation.

The Y-chromosome STR study disclosed that 50% of patients showed paternal origin belonging to haplogroup R1b (found in Portuguese and Spanish populations) and 40% belonged to haplogroups J and E (typical in the Middle East and in Eastern European Jews). mtDNA analysis showed that 29% of patients belonged to the Amerindian haplogroup B, 18% had European haplogroup J (from the Balkan Peninsula), 35% presented African haplotypes, and the Israeli patient showed subhaplogroup R0 found in Arabia. Lineage markers, Y-chromosome, and mitochondrial DNA are uniparentally inherited markers that are frequently used in phylogenetic studies to trace human migrations [Underhill and Kivisild, 2007].

The Y-DNA haplogroup R may be the most numerous Y-DNA in the world today. The origin of haplogroup R is located in Central to West Asia, although a precise region has not yet been determined. The R1b branch is the most abundant haplotype identified in South American countries [Guerra et al., 2011; Francez et al., 2012; Watkins et al., 2012], consistent with historical accounts of male admixture in colonies of Spain and Portugal, where this haplogroup

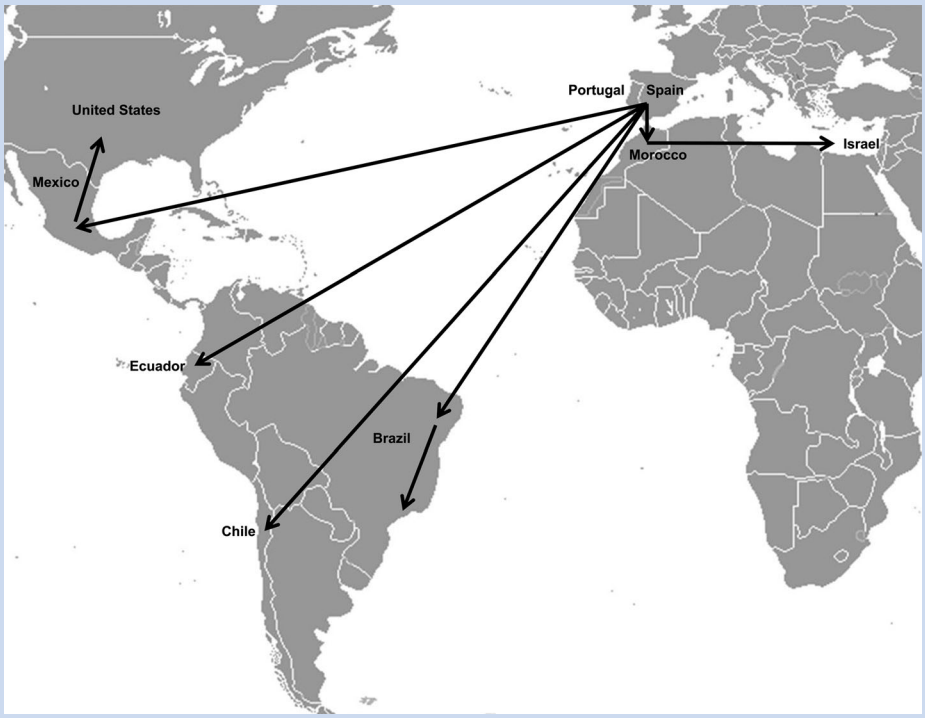

FIG. 1. Partial world map showing the possible migration route of Iberian Jewish descent carrying E180splice mutation in *GHR* from the Iberian Peninsula to the Americas and Israel.

is common [Adams et al., 2008]. However, the haplogroups E1 and J, also found in our patients, are infrequently observed in the Iberian Peninsula. The haplogroup J is the main haplotype (47%) found in the Sephardic Jewish population [Adams et al., 2008].

The maternal lineage origin analysis by mtDNA presented haplotypes from Haplogroup J, which is found in 7% of the Jewish population, Haplogroup L, found also in Moors and Jews from Portugal in the 14th and 15th century, and Haplogroup B, an Amerindian haplogroup. These findings suggest that the matrilinear inheritance was the result of a two-way admixture model between European-derived populations (including *Sephardim*) and Native Americans, as observed in other modern Latin American populations from Colorado and Ecuador [Velez et al., 2012].

In conclusion, we have provided additional evidence of co-segregation between several polymorphic markers and the germline *E180Splice* mutation, indicating that this mutation probably originated from a single common ancestor of these individuals. The presence of Y-chromosome markers associated with Sephardic populations in persons harboring the E180splice mutation provides genetic evidence in support of the historical tracking of the exodus of this specific population.

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