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Gaucher Disease: The N370S Mutation in Ashkenazi Jewish and Spanish Patients has a Common Origin and Arose Several Thousand Years Ago

To the Editor:

The identification of highly polymorphic markers, which are widely distributed throughout the human genome, has allowed the mapping of several disease genes. These markers have been used to analyze the origin, in time and place, of the most prevalent mutations for different diseases, such as cystic fibrosis (Morral et al. 1994), idiopathic torsion dystonia (Risch et al. 1995), hereditary colon cancer (Moisio et al. 1996), factor XI deficiency (Peretz et al. 1997), and myotonic dystrophy (Tishkoff et al. 1998). We present the analysis of the origin of N370S, the most common Gaucher disease (GD) mutation among Ashkenazi Jewish and Spanish patients. The results show that both patient populations share the same ancestral haplotype and that this mutation arose several thousand years ago.

GD (MIM 230800), caused by mutations in the glucocerebrosidase (*GBA*) gene, is the most prevalent lysosomal storage disease. It is inherited as an autosomal recessive trait, which is particularly frequent in the Ashkenazi Jewish population, with a disease incidence of ~1/850 (Beutler and Grabowski 1995). It is also found in other populations, albeit with lower frequency, with a range of 1/40,000–1/60,000 (Grabowski 1993). Among Ashkenazi Jewish patients with GD, ~70% of the alleles carry the N370S (1226A→G) mutation (Beutler et al. 1992*a*; Horowitz et al. 1993; Sibille et al. 1993). It appears that approximately two-thirds of the individuals homozygous for this mutation escape detection because of the very mild clinical manifestation; thus, the N370S frequency in the Ashkenazi Jewish population is higher, ~90% of all GD mutations (Beutler et al. 1993; Grabowski 1997). This mutation is also frequent

in other populations of patients with GD, particularly among Spanish patients, in whom it accounts for > 40% of the mutant alleles (Cormand et al. 1995, 1998).

We have recently mapped the *GBA* gene in relation to several highly polymorphic markers (Cormand et al. 1997), which were then used to identify a putative ancestral haplotype associated with the N370S mutation in chromosomes from Spanish patients (Cormand et al. 1998). Preliminary studies of a few Argentinian patients with GD, of Ashkenazi Jewish origin, showed that they have the same conserved haplotype as the Spanish patients with GD. This prompted us to perform the present study on DNA isolated from 66 unrelated Ashkenazi Jewish patients with GD of central and eastern European descent living in the United States, who were evaluated at the New York University Medical Center, and 14 Spanish patients with GD who were referred from different hospitals around Spain and enzymatically diagnosed at the Institut de Bioquímica Clínica in Barcelona. Both groups of patients bore the N370S mutation. A total of 104 N370S Ashkenazi Jewish chromosomes and 20 N370S Spanish chromosomes were analyzed. Forty healthy Ashkenazi Jewish individuals from the United States were used as controls, and CEPH family data were used as non-Jewish controls. The distances (in terms of recombination fractions [θ]) between the markers used for haplotyping and the *GBA* gene (Cormand et al. 1997) are shown in table 1. Linkage analysis between the *GBA* gene and one of these markers, *D1S1595,* has not been previously described (maximum LOD score of 9.33 at $\theta = .00$). Since meiotic mapping showed insufficient resolution capacity for markers closest to the *GBA* gene (*D1S2140, D1S2777, D1S1595,* and *D1S2721*), the Stanford G3 radiation hybrid (RH) panel (Research Genetics) was used to estimate the distances between these markers and the *GBA* gene. Following Cox et al. (1990) and Moisio et al. (1996), a 1 cR/50 kb ratio was used to calculate the distance in centimorgans (900 kb/1 cM), which we transformed into θ values using the Haldane map function. Hybrid DNA was amplified by PCR using standard protocols. Primers used to detect the presence of the *GBA* gene were as follows: forward, 5′-AACCATGATTCCCTATCTTC-3′; reverse, 5′-GAGGCACATCCTTAGAGGAG-3′. As noted by Moisio et al. (1996), RH mapping generally yields greater distances between marker loci than does meiotic mapping.

Previously, we reported a common disease haplotype in Spanish patients with GD bearing the N370S mutation (Cormand et al. 1998). Analyses of 66 Ashkenazi Jewish patients and five additional Spanish patients with GD, using six microsatellite markers, revealed that most of the Jewish and Spanish N370S chromosomes share alleles for five of these markers. Figure 1*a* shows the haplotype of the 73 Ashkenazi Jewish N370S chromosomes, of the 104 analyzed, for which the phase had been established for all the markers (phases were determined by use of samples from parents and/or siblings). Forty-three (59%) have a conserved haplotype for markers *D1S2140, D1S2777, D1S1595, D1S2721,* and *D1S2624*. Marker *D1S305* presented many different alleles and was not included in figure 1, to allow sample grouping. If the more distant marker D1S2624 (see meiotic mapping, table 1) is excluded, the proportion of chromosomes with a conserved haplotype rises to 68 (93%) of 73. If only the three markers closest to *GBA—D1S2140, D1S2777,* and *D1S1595,* according to RH mapping (see table 1)—are considered, this proportion is increased to 69 (94.6%) of 73. The same analysis of 18 Spanish N370S chromosomes for which the phase is known, is shown in figure 1*b*. Two chromosomes were excluded because phase could not be established for all the markers. The haplotype for the three closest markers mentioned above is conserved in 16

Table 1

Distances by RH and Meiotic Mapping between the *GBA* Gene and 1q21 Markers and Estimated Age of the N370S Mutation

	RH Mapping		Meiotic Mapping	
Marker	Distance (cR/θ[a])	Age of the Mutation (Years/Generations)[b]	Distance (θ)	Age of the Mutation (Years /Generations)[b]
D1S305	45.0/.024	1,100/44	.023	1,300/52
D1S2140	39.4/.022	2,675/107	.0	…
D1S2777	19.8/.011	12,675/507	.0	…
D1S1595	43.8/.024	3,125/125	.0	…
D1S2721	55.0/.030	950/38	.0	…
D1S2624	67.2/.037	4,225/169	.025	9,525/381

[a] Obtained from the cR value, assuming 1 cR = 50 kb and 900 kb = 1 cM, and then by use of Haldane map function.

[b] Age of the mutation estimated in number of generations, by use of the formula by Risch et al. (1995). Years calculated assuming 25 years/generation.

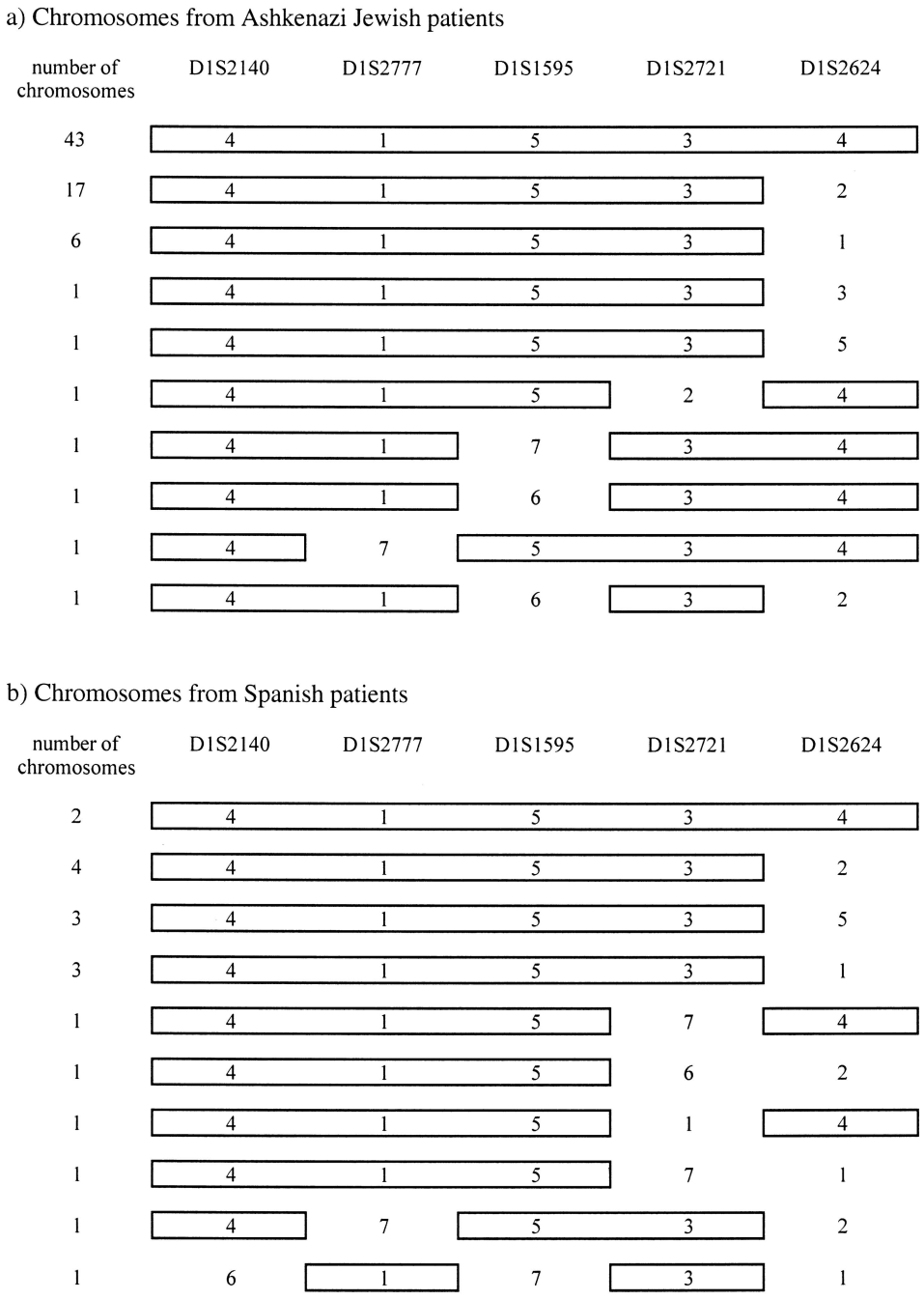

Figure 1 Haplotype analysis for 1q21 markers. *a*, Chromosomes from Ashkenazi Jewish patients with GD bearing the N370S mutation. *b*, Spanish patients with GD bearing the N370S mutation. Both groups were analyzed for markers *D1S2140, D1S2777, D1S1595, D1S2721,* and *D1S2624*. The conserved parts of the haplotypes are boxed.

(88.9%) of 18 of the chromosomes. In addition, all Ashkenazi Jewish and Spanish N370S alleles bear the "−" allele for the *Hba*I site (data not shown), which corresponds to an adenine at genomic position 6144, one of the *GBA* internal polymorphisms (Beutler et al. 1992*b*).

Table 2 shows the allele frequencies and linkage disequilibrium (LD) analysis for markers in chromosomes bearing the N370S mutation in Ashkenazi Jewish and Spanish patients and in the control population. The degree of LD was assessed by the parameter δ [$\delta =$

Table 2

Haplotype and LD Analyses in N370S Chromosomes of Ashkenazi Jewish and Spanish Patients

		Frequency of Ashkenazi Jewish Chromosomes				Frequency of Spanish Chromosomes			
Marker	Allele	N370S	Controls	χ^2 (P value)	δ	N370S	Controls[a]	χ^2 (P value)	δ
D1S305	1	58.6 (41/70)	40.0 (32/80)	5.2 ($P<.05$)	.31	47.4 (9/19)	23.2 (13/56)	4.0 ($P<.05$)	.31
D1S2140	4	95.6 (86/90)	47.5 (38/80)	49.6 ($P<.001$)	.92	90.0 (18/20)	30.4 (17/56)	21.1 ($P<.001$)	.86
D1S2777	1	97.8 (89/91)	63.8 (51/80)	33.3 ($P<.001$)	.94	90.0 (18/20)	57.1 (32/56)	7.1 ($P<.01$)	.77
D1S1595	5	92.8 (77/83)	45.0 (36/80)	43.7 ($P<.001$)	.87	90.0 (18/20)	28.2 (35/124)	28.3 ($P<.001$)	.86
D1S2721	3	93.6 (88/94)	33.8 (27/80)	69.1 ($P<.001$)	.90	70.0 (14/20)	23.1 (12/52)	13.8 ($P<.001$)	.61
D1S2624	4	57.8 (52/90)	20.0 (16/80)	25.2 ($P<.001$)	.47	20.0 (4/20)	17.9 (10/56)	.05 (NS)[b]	.03

[a] CEPH data.
[b] NS = not significant.

$(p_D - p_N)/(1 - p_N)]$, in which p_D is the frequency of the associated allele on disease chromosomes and p_N is the frequency of the same allele on normal chromosomes, as in the study by Risch et al. (1995), and statistical significance was measured by the χ^2 test. All markers were found to be in strong LD with the N370S mutation in Ashkenazi Jewish patients ($P < .001$), except marker *D1S305,* for which the significance is very low ($P < .05$). For the Spanish chromosomes, only the central markers (*D1S2140, D1S2777, D1S1595,* and *D1S2721*) are in marked LD with the N370S mutation. The fact that the highest values of δ, in both patient populations, correspond to markers *D1S2140, D1S2777, D1S1595,* and *D1S2721,* is consistent with meiotic mapping, which places the *GBA* gene at a distance of $\theta = .0$ (see table 1). LD for the five markers (all except *D1S305*) was confirmed in the Ashkenazi Jewish patients, with the $D' = D/D_{max}$ standardized coefficient (Lewontin 1988) and the likelihood ratio test described by Terwilliger (1995) (data not shown), since this information was relevant for the dating analysis.

To date the N370S mutation among the Ashkenazi Jewish patients, we applied the following formula by Risch et al. (1995):

$$g = \frac{\log[(1 - Q)/(1 - p_N)]}{\log(1 - \theta)} \cdot \frac{\log(\delta)}{\log(1 - \theta)},$$

in which g is the number of generations, Q is the probability that an N370S-bearing chromosome does not carry a progenitor marker allele, and p_N and δ are as described above. The estimation of the age of the mutation is based on the calculated distance between the gene of interest and the flanking markers. Marker *D1S2624* is the only one for which the distance to the gene could be estimated by both meiotic and RH mapping (table 1), and it is in LD with the mutation (marker *D1S305* is not). Using these estimated distances for marker *D1S2624,* we obtained a result of 381 or 169 generations, respectively, and, assuming 25 years/generation, an estimated age for the N370S mutation of ~9,500 or 4,200 years, with an average of ~7,000 years. The values for the rest of the markers are shown in table 1.

To conclude, a similar haplotype was found to be associated with the common N370S mutation in the Spanish and Ashkenazi Jewish patients. This suggests a common origin for the mutation. The high frequency of particular mutations among Ashkenazi Jews has been explained either by a selective advantage of heterozygote carriers or by a founder effect and genetic drift (Motulsky 1995; Peretz et al. 1997). Our data strongly support a founder effect as opposed to recurrence of the N370S mutation: all the chromosomes with this mutation had the "−" allele for the *GBA* internal *Hba*I-site polymorphism, and most of them share the alleles for several markers close to the gene. The few exceptions could be explained by historic recombinations. Although a new occurrence of N370S cannot be ruled out, it seems very unlikely. If we assume a founder effect, both genetic drift and selective advantage could explain the expansion of the mutated allele in the population. Our data do not contribute to this discussion, which is beyond the scope of the present work.

Several studies have attempted to date mutations for diseases that are prevalent among the Ashkenazi Jews, such as idiopathic torsion dystonia (Risch et al. 1995), familial dysautonomia (Blumenfeld et al. 1993), Bloom syndrome (Ellis et al. 1994), and factor XI deficiency (Peretz et al. 1997). Whereas the dystonia mutation seems to have occurred ~300 years ago, one of the mutations causing factor XI deficiency is supposed to be quite old (>2,000 years), as determined on the basis of the shared haplotype found among Ashkenazi and Iraqi Jews.

Our data provide information on the most frequent mutation in GD, N370S, which occurred several thousand years ago. It should be noted that the method of dating the mutation is subject to statistical fluctuation resulting from sampling variance and from uncertainty

in the estimates of θ (Risch et al. 1995); therefore any accuracy beyond an estimation of several thousand years for the age of the mutation is meaningless. However, the relatively short length of the chromosomal region in which LD is conserved strongly supports the idea of an ancient origin for the N370S mutation.

The data presented here suggest a common origin for this mutation in the Ashkenazi Jewish and Spanish patient populations. It could be speculated that the Spanish N370S chromosomes derive from Jewish alleles, since this mutation, very prevalent among Ashkenazi Jews, is more frequent in Spain (Cormand et al. 1998) and Portugal (Amaral et al. 1996) than in the rest of Europe and since it is known that many Jews converted to Catholicism by the time of their expulsion from Spain in the 15th century. Although Jewish individuals from the Iberian Peninsula are believed to be of Sephardic origin, the results of haplotype analysis for the Ashkenazi Jewish chromosomes in our study suggest that the mutation may have been introduced before the Ashkenazim and Sephardim became relatively independent populations. This event took place ~800–1,000 years ago (Baron 1968; Ankori 1979), although contacts between the two communities are known to have occurred after that time.

Against the hypothesis of a Jewish origin for the Spanish N370S chromosomes is the fact that overall LD values are lower among Spanish than among Ashkenazi Jewish chromosomes (table 2). Because lower LD values are indicative of a larger number of generations (Jorde 1995), our data support the hypothesis of an ancient European, non-Jewish origin of the "Spanish" mutation. Conversion of pagans to Judaism during the Roman period could be an explanation for a possible way by which the mutation could have entered the Jewish population. The preliminary data presented recently by Díaz et al. (1998), showing that Ashkenazi Jewish N370S chromosomes have higher LD values than those found in Portuguese and French N370S chromosomes, are consistent with the data presented here. The analysis of N370S haplotypes in Sephardim and in other European populations would be extremely useful, to clarify this issue.

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Electronic-Database Information

Accession number and URLs for data in this article are as follows:

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Deafness Locus DFNB16 Is Located on Chromosome 15q13-q21 within a 5-cM Interval Flanked by Markers D15S994 and D15S132

To the Editor:

Inherited human deafness has an incidence of ~1/2,000 births (Cohen and Gorlin 1995). The hearing impairment can be associated with other clinical features as part of a distinct syndrome, but in most cases (70%) it is the sole clinical sign (Bergstrom et al. 1971). Autosomal recessive transmission accounts for ⩽85% of nonsyndromic sensorineural deafness (Cohen and Gorlin 1995). Nonsyndromic autosomal recessive deafness is clinically homogeneous; in most cases, the hearing loss has a prelingual onset, involves all the frequencies, is severe or profound, and is nonprogressive (Van Camp et al. 1997). However, as expected from the structural and functional complexity of the inner ear, sensorineural deafness exhibits a very high genetic heterogeneity. Nineteen loci for autosomal recessive hearing loss have been mapped, to date (Hereditary Hearing Loss home page). One of these loci, DFNB16, was mapped to chromosome 15q21-22 by linkage studies of three consanguineous families from Pakistan, Palestine, and Syria (Campbell et al. 1997). Analysis of recombinant haplotypes indicated that the locus was in a 20-cM interval delimited by markers D15S994 and D15S155. Acting on the results of homozygosity data, Campbell et al. (1997) narrowed the location of DFNB16 to the 15-cM distal part of the interval, between markers D15S1039 and D15S155. The pedigree and haplotype analysis of family S040 (fig. 1) provides evidence against the last conclusion. Our work locates DFNB16 to the proximal 5-cM part of the interval, between D15S1044 and D15S132.

Informed consent was obtained from all the individuals included in the study. All the family members underwent a clinical examination. Environmental factors were eliminated as the cause of deafness in all affected family members. There were no features suggestive of ophthalmologic, skin, or renal syndromic anomalies. Conductive hearing loss was ruled out by otoscopic examination, tympanometry with acoustic reflex testing, and use of the tuning fork test. Pure-tone audiometry was performed to test for air conduction (frequencies of