Letters to the Editor

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The African Origin of the Common Mutation in African American Patients with Glycogen-Storage Disease Type II

To the Editor:

Conventional historiographical research provides abundant evidence of the African roots of African American populations, but, because of the absence of complete documentary records—for example, the point of embarkation of a particular slave vessel does not necessarily indicate who was actually on that vessel, and slave cargoes tended to be composed of mixed populations—it remains a frustrating task to identify exactly who was transported to the Americas (Curtin 1969; Parish 1989; Thornton 1992). The presence of a genetic marker in an African American population, however, might furnish a verifiable link, for the individuals who carry the trait, to a specific tribe or even to a point of origin.

In the autosomal recessive disorder glycogen-storage disease type II (GSD II [MIM 232300]), a deficiency of acid maltase (GAA; acid α-glucosidase) leads to the pathological accumulation of glycogen in lysosomes. In its most severe form, progressive cardiomyopathy causes cardiorespiratory failure and death within the 1st year of life (Pompe syndrome). Among the mutations identified (see Lin and Shieh 1995; Raben et al. 1995; Tsunoda et al. 1996; Adams et al. 1997; reviewed by Reuser et al. 1995; Hirschhorn and Huie 1997), three that lead to the total loss of enzyme activity occur frequently in particular ethnic groups: deletion of exon 18 in Caucasians (Boerkoel et al. 1992; Huie et al. 1994*a;* Van der Kraan et al. 1994; Kroos et al. 1995), deletion of T525 in northern Europeans (Hermans et al. 1994; Kroos et al. 1995), and D645E in Chinese patients from Taiwan (Shieh et al. 1994; Lin and Shieh 1996). The chance to study several affected infants of African parents has permitted us to identify a common African mutation, to confirm our previous suggestion that the mutation is also common in African Americans (Adams et al. 1997), and, thereby, to explore the molecular roots of GSD II in African Americans.

We initially studied a 3-mo-old infant (patient 1), from the Ivory Coast, of healthy, nonconsanguineous parents; the mother is Mandingo, and the father is Guéré (table 1). The patient is a compound heterozygote harboring a previously described C2560T transition in exon 18 (Hermans et al. 1993*a;* Adams et al. 1997) and a novel T2846A transversion in exon 20. An unusual feature of the novel exon 20 mutation (V949D) is its localization at the carboxy terminus of the 952 amino acid precursor, the tail that is removed during processing into mature forms (Wisselaar et al. 1993). Expression studies showed that the mutation results in complete inactivation of the enzyme: catalytic activity of the mutant protein in transfected COS cells did not exceed the background levels—778, 30, and 26 nmol 4-4-methylumbelliferone/h/mg cell protein for the wild-type, mutant, and mock-transfected cells, respectively. The mature protein was not detected by western analysis, thereby adequately explaining the absence of enzyme activity in this allele (data not shown). Apparently, the mutation results in a degradation of the precursor molecules prior to processing and maturation.

The paternally inherited nonsense mutation in exon 18 (R854X), which resides on a silent allele, had been previously described in a compound-heterozygous adult African American patient (cell line GM 01935) (Hermans et al. 1993*a*) and in a half–African American (African American father and Caucasian mother) child (patient 6) with the juvenile form of the disease (table 1). The data thus strongly pointed to an African origin of the R854X mutation in the African Americans and prompted us to look for more patients of a similar background. Two other infants born of western African parents were available for study. The R854X mutation was present on one allele of a 2-mo-old infant (patient 2) of healthy, nonconsanguineous parents who were of Hausa origin. One parent was from the province of Katsina, and the other was from the northeastern Borno province (parental DNAs were not available); the patient's male sibling had died at age 5 mo, of unknown causes. Both alleles of a 4-mo-old Ghanaian infant (patient 3) of healthy, nonconsanguineous parents, who were from the Twi subgroup of the Ashanti tribe and were living in Accra, bore R854X. We also sought the mutation in infants of different backgrounds who were from southern Africa and who had been reported by van der Ploeg

Table 1

Presence of R854X or Other Mutations on African or African American Chromosomes

Group and Patient	Mutation Status of	
	Chromosome 1	Chromosome 2
African:		
Patient 1 (Ivory Coast)	R854X	V949D
Patient 2 (Nigeria)	R854X	Negative[a]
Patient 3 (Ghana)	R854X	R854X
Patient 4 (Ovambo-Namibia)	R854X	R854X
Patient 5 (Zulu-South Africa)	Negative	Negative
African American:[b]		
Patient 6 (mixed)	R854X	IVS6 −22 t→g
Patient 7	R854X	Negative
Patient 8	R854X	Negative
Patient 9 (C2123)	R854X	R854X
Patient 10 (C1992)	Negative	Negative
Patient 11 (C9752)	Negative	Negative
GM 00248	R854X	R854X
GM 00338	R854X	R854X
GM 01935	R854X	D654E
GM 03329	Negative	M519V
GM 04912	Negative	Negative
GM 12932	Negative	Negative

Note.—This study was carried out under protocols approved by the institutional review boards of the National Institute of Arthritis and Musculoskeletal and Skin Diseases and of the institutions where the samples were obtained. Details of the primers, PCR conditions, and identification of mutations are available on request.

[a] R854X not present.

[b] Patient 6 has been reported in detail elsewhere (Adams et al. 1997). Patient 7 was the 6-wk-old daughter of healthy, nonconsanguineous African American parents; patient 8 was a 6-mo-old African American male referred to New York University Medical Center by Dr. H. Mussel; patients 9–11 (C2123, C1992, and C9752) were referred to the New York State Institute for Basic Research and New York University Medical Center. The cell lines designated "GM" were obtained from the National Institutes of Health Mutant Repository, Coriell Cell Repositories (Camden, NJ) and were derived from African American patients with infantile-onset GSD II (GM 00248, GM 12932, GM 03329, GM 00338, and GM 04912) (Martiniuk et al. 1986; Zhong et al. 1991) or adult-onset GSD II (GM 01935). Additional clinical information is present in the Coriell catalogue. Mutations and additional molecular information have been reported for GM 03329 (Huie et al. 1994*b*) and GM 01935 (Martiniuk et al. 1991; Hermans et al. 1993*a*). The diagnosis of severe deficiency of GAA was demonstrated in each of these patients by enzymatic assay of fibroblasts and/or muscle.

et al. (1989). Both alleles of an Ovambo infant (patient 4) from Namibia carried R854X, and a Zulu infant (patient 5) was negative. (R854X was also absent in the two infants from southern Africa who were of uncertain ethnic background.) R854X was present, therefore, in four of five African infants of known ethnic background, on 6 of 10 chromosomes.

Among the 12 African American patients studied (patients 6–11 and six GM cell lines), 3 are homozygous, and 4 are heterozygous, for R854X (table 1). Therefore, 10 of 23 African American chromosomes (the mother of patient 6 is Caucasian) carry the R854X mutation, resulting in an allele frequency of .43 among African Americans with GSD II.

The other mutation described in an African American (Hermans et al. 1993*a*) and also identified in Chinese patients—that is, D645E—was not found in any of our cases. In African American patients (Hermans et al. 1993*b*) but not Chinese patients (C-Y Lin, personal communication), the mutation is associated with two polymorphic sites in exons 17 and 19 (I816 and I927) found in several healthy unrelated African Americans, suggesting that the Chinese and African American D645E mutations occurred independently. By contrast, all eight polymorphic sites (596G, 668A, 921T, 1203A, 1374T, 2154C, 2338A, and 2553A) residing on the R854X mutated African American allele in our juvenile case (Adams et al. 1997) are identical to those found in the infants from the Ivory Coast, Ghana, and Namibia, a finding that suggests a common haplotype and a common origin of the R854X mutation.

The R854X mutation was not found in 7 infantile- and 34 adult-onset Caucasian patients with GSD II. This represents 48 chromosomes at risk for a "null" mutation: 2 from each infant and only 1 from each adult, since adult patients have some enzyme activity. These results clearly document that R854X is not frequent in all populations. However, the mutation was found in homozygosity in an infantile patient from consanguineous Pakistani parents and was found in heterozygosity in a Mexican American patient and in a French patient. The R854X mutation is a C→T transition at a CG dinucleotide and therefore is at a site susceptible to recurrent mutations. Further investigation of haplotypes could reveal whether these are independently recurring events.

Of the 12 million African captives, <600,000 ever reached North American shores. The slave trade to North America experienced two particularly strong periods: one just before the American Revolution of 1776, and the second at the turn of the 19th century, just before the passage, in 1808, of a law prohibiting the importation of African slaves (Rawley 1985). The first Africans to be enslaved in the 16th century were peoples from the western Atlantic region. Traders then worked their way incrementally along the coast, focusing next on Guinea Coast peoples, and, at the height of the late-18th century trade, peoples of the Guinea Coast, often of Ashanti origin, were most common in slave cargoes. The trade eventually reached Angola, around 1800 (Curtin 1969).

The four African ethnic groups currently known to carry R854X (fig. 1) have a history of long-standing interaction. The Hausa, although they claim northern Nigeria as their homeland, are widely dispersed throughout western Africa. Their commercial activities, initiated as early as 1100, brought them into direct and prolonged

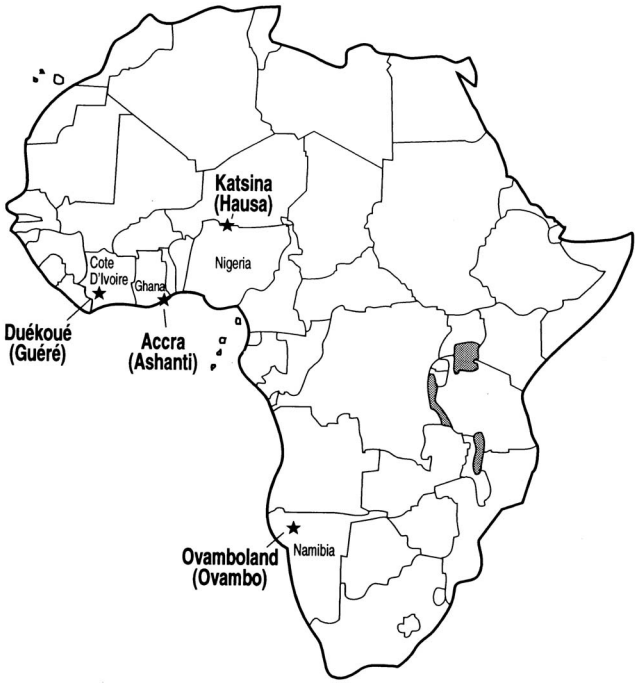

Figure 1 Geographic location of western African populations described in the text.

contact with the western Atlantic region, where they encountered the Guéré of the Ivory Coast. The Guéré, in turn, were a subgroup of the Kru who, because of their boating skills, were used as deckhands on European trading vessels sailing in Africa's coastal waters. The Hausa also had strong contacts with the Ashanti nation, in what is today the nation of Ghana, both through trade connections and through residential enclaves. The Ovambo of Namibia, although they were beyond the reach of the Hausa trade network, are a Bantu-speaking group descended from a population originally located on the Bauchi plateau of northern Nigeria, adjacent to the Hausa homelands. Segments of this Nigerian group, who would eventually become the Ovambo, undertook a gradual southward migration that brought them to their current location in Angola and northern Namibia, sometime during the period of 800–900 (Turnbull 1977; Curtin and Bohannon 1988). Thus, although it is probable that the closest African ancestors of the African American patients were culturally Ashanti and were brought to North America from the Guinea Coast, their genetic makeup strongly suggests that they have Hausa roots. It is reasonable to speculate that the mutation occurred some time before the southward migration of the Ovambo away from the territory of the Hausas, possibly in their common ancestral population from north-central Africa.

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