Letters to the Editor

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Variant 1859G→A (Arg620Gln) of the "Hairless" Gene: Absence of Association with Papular Atrichia or Androgenetic Alopecia

To the Editor:

Recent studies have shown that mutations in the human "hairless" gene (*HR*) are responsible for complete, congenital absence of hair in families with autosomal recessive universal congenital alopecia (ALUNC [MIM 203655]) and autosomal recessive papular atrichia (APL [MIM 209500]) (for review, see Kruse et al. 1999). In the October 1998 issue of the Journal, Ahmad et al. (1998) reported that a missense mutation (1859G→A, which results in Arg620Gln) in the zinc-finger domain caused papular atrichia among members of a family of Irish descent. Evidence that Gln620 represents a disease-causing mutation was based on the following four observations (Ahmad et al. 1998): (1) Gln620 was found in a homozygous state only in affected family members, (2) Gln620 was not observed in 50 unaffected control individuals, (3) Arg620 is located in the zinc-finger domain of *HR*, and (4) Arg620 is conserved among human, mouse, and rat genes.

We recently conducted a mutation screen of *HR* in 46 individuals with androgenetic alopecia (AGA) (A.M. Hillmer, R. Kruse, F. Macciardi, U. Heyn, R.C. Betz, T. Ruzicka, P. Propping, M.M. Nöthen, S. Cichon, unpublished data). Unexpectedly, we detected one individual who was heterozygous for Arg620Gln. Because this observation raised the possibility that Arg620Gln may be a polymorphism and not a disease-causing mutation, we tested for the presence of Arg620Gln in a further 820 individuals of various ethnic origins: 601 from Germany (comprising 288 individuals recruited among laboratory staff and students, 198 anonymous blood donors, 57 individuals with AGA, and 58 control individuals without AGA), 79 from Japan, 65 from Oman, 49 from Mexico, and 26 from Pakistan. In all individuals, exon 6 of *HR* was amplified from genomic DNA, using a nested PCR approach. In a first PCR, primers Ex6MutF1 (5′-GGA GGT GGA GGA AAG AAT GTG C-3′) and Ex6MutR1 (5′-CTG CAG AGA GGG GAA GTC TGC T-3′) were used to generate a 686-bp PCR product comprising exon 6 and flanking intronic sequences. To enhance the specificity and yield of the reaction, 1 μl of the PCR product was used for a second PCR, with primers Ex6MutF2 (5′-ATG GAA GCT GCT CCT TGC TTC-3′) and Ex6MutR2 (5′-GTA GGG GGC TTT TTG GGG AG-3′), which gave a 380-bp PCR product. Tests for the presence of the mutation were conducted after digestion with restriction endonuclease *Pvu*II, as described by Ahmad et al. (1998).

Among 820 individuals, we identified 44 who were heterozygous for Arg620Gln and 1 who was homozygous for Gln620. These alleles were distributed among the ethnic groups as follows: among Germans, allele Gln620 was found in 33 individuals in a heterozygous state and in 1 individual (ANA 87-01) in a homozygous state, resulting in a Gln620 allele frequency of 2.7%; heterozygosity for Gln620 was detected in 5 individuals from Oman, 3 from Pakistan, and 3 from Mexico, resulting in allele frequencies of 3.8%, 5.8%, and 3.1%, respectively. Gln620 was not detected among the 79 individuals from Japan.

Homozygosity for Gln620 in individual ANA 87-01 was verified by sequence analysis (fig. 1*A*) and *Pvu*II digestion (fig. 1*B*) of a 119-bp PCR-fragment directly amplified from genomic DNA with primers HREx6internF (5′-CCA CCA TGG ACT CTT CAA CA-3′) and HREx6internR (5′-CCC CTC TCC TAC CTG CTT T-3′). In addition, to check for Mendelian inheritance, we investigated DNA samples of the parents and brother of ANA 87-01. Both parents (ANA 87-02 and ANA 87-03) are heterozygous (Arg620/Gln620), and the brother (87-04) is homozygous for allele Arg620 (fig. 1*B*). To exclude allele-specific amplification of the exon 6–bearing allele Gln620, the binding sites of primers HREx6internF, Ex6MutF1, Ex6MutF2, Ex6MutR1, Ex6MutR2, and HREx6internR were sequenced in ANA 87-01. We observed no mutation in the primer binding sites. Furthermore, we genotyped seven microsatellite markers (D8S550, LPL, D8S258, D8S280, D8S282, D8S283, and D8S285) flanking *HR* in family ANA 87. The parents had four distinguishable haplotypes. ANA 87-01 showed two different haplotypes that were distinct from the two haplotypes of his brother ANA 87-04. These results confirm the transmission of two parental Gln620 alleles to ANA 87-01 and two Arg620 alleles to ANA 87-04.

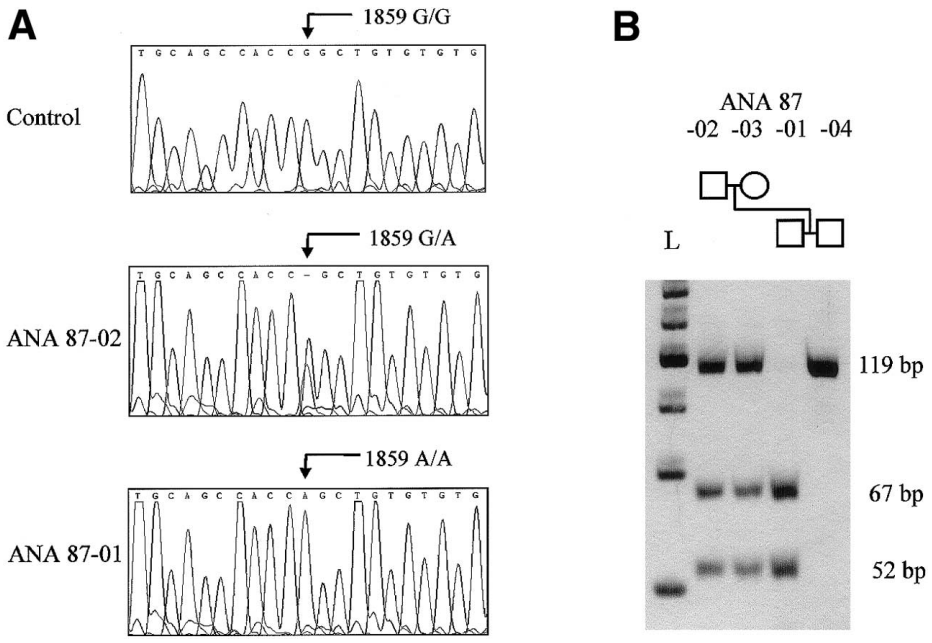

Figure 1 Genotyping of the 1859G→A (Arg620Gln) variant in exon 6 of *HR*. *A,* Sequence analysis of exon 6 of a control individual (*top*) with the genotype 1859G/G, individual ANA 87-02 (*middle*) with the genotype 1859G/A, and individual ANA 87-01 (*bottom*) with the genotype 1859A/A. *B, Pvu*II RFLP analysis of a 119-bp PCR fragment that contains exon 6 of *HR* (including nucleotide position 1859) in four members of family ANA 87. Fragments were separated on a 10% polyacrylamide gel and visualized by silver staining. Allele 1859G remains uncut (119-bp fragment), and allele 1859A produces a 67-bp and a 52-bp fragment. ANA 87-01 is homozygous for allele 1859A, and the brother, ANA 87-04, is homozygous for allele 1859G. The parents, ANA 87-02 and ANA 87-03, are heterozygous for 1859G/A. *Lane L,* 25-bp ladder (Gibco).

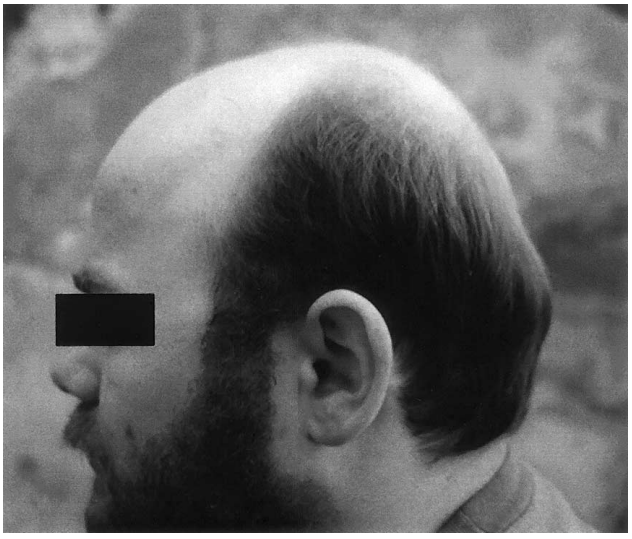

Figure 2 Phenotypic appearance of individual ANA 87-01, who is homozygous for 1859A (Gln620) of *HR*. He displays androgenetic alopecia but is clearly not affected with papular atrichia. The hair of the scalp and beard (as well as the rest of the body hair) is normally developed, and there are no signs of papular rash.

For the two reasons, our results lead to the conclusion that Arg620Gln is indeed not a disease-causing mutation but a polymorphism without consequences for hair development. (1) Given a Gln620 allele frequency of 2.7%, one would expect almost 60,000 individuals affected with APL in Germany; however, no German has yet been reported to be affected with this disease. (2) We identified an individual who is homozygous for Gln620 but, unambiguously, is not affected with papular atrichia. Male-pattern loss of scalp hair started at the age of 18–20 years. He developed severe androgenetic alopecia (Norwood-Hamilton grade VI) by the age of 26 years. Figure 2 shows the individual at the age of 33 years. The rest of the scalp hair, eyebrows, and beard hair, as well as pubic, axillary, and body hair developed normally and remained completely normal. There are no signs of a papular rash.

In the family of Irish Travellers reported by Ahmad et al. (1998), Arg620Gln cosegregates with papular atrichia. In the light of our findings, however, it must be concluded that it is a polymorphism in close linkage with a yet unidentified disease-causing mutation at the *HR* locus in the reported family. An alternative explanation

of the discrepancy between results of our study and those of the report by Ahmad et al. (1998) would be the existence of modifier genes. However, this is very unlikely, given the fact that none of the reported molecular studies of families with APL has observed a case of incomplete penetrance.

Interestingly, although the individual who is homozygous for Gln620 is not affected with papular atrichia, he displays AGA. We therefore examined the frequency of Gln620 in a sample of 103 males with severe AGA and in 58 males (age > 60 years) without AGA. Allele frequencies were similar in both groups (2.91% and 3.45%, respectively; $P = .79$), which suggests that Arg620Gln does not play a role in the development of AGA.

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The Presence of Mitochondrial Haplogroup X in Altaians from South Siberia

To the Editor:

For American Indians, extensive RFLP and HVSI sequence analysis has unambiguously identified four major founding mtDNA haplogroups (A, B, C, D), which account together for ~97% of modern American Indian mtDNAs (Wallace 1995). Examination of the distribution of the four founding lineage haplotypes (A, B, C, and D) in American Indian populations (both contemporary and ancient) shows that all four lineages were present in the New World prior to European contact (Wallace 1995; Lalueza et al. 1997; Stone and Stoneking 1998), thus indicating that all American Indian mtDNAs are apparently descended from these four founding lineages. mtDNAs apparently not from haplogroups A–D may result from recent admixture with non–American Indians or may represent additional American Indian founding mtDNA lineages.

A striking example of the presence in American Indians of genotypes not from haplogroups A–D is haplogroup X. This haplogroup represents a minor founding lineage that is restricted in distribution to northern Amerindian groups, including the Ojibwa, the Nuu-Chah-Nulth, the Sioux, and the Yakima, as well as the Na Dene–speaking Navajo (Brown et al. 1998). Unlike haplogroups A–D, haplogroup X is also found at low frequencies of ~4% in western Eurasian populations. Despite a shared consensus RFLP haplotype, substantial genetic differences exist between the American Indian and European haplogroup X mtDNAs. Phylogenetic analysis and coalescence estimates for American Indian and European haplogroup X mtDNAs exclude the possibility that the occurrence of haplogroup X in American Indians is due to recent European admixture. They also clearly indicate that the two branches/subgroups are distantly related to each other and that considerable genetic substructure exists within both groups (Brown et al. 1998).

Haplogroup X is remarkable in that it has not been found in Asians, including Siberians, suggesting that it

Table 1

RFLP and HVSI, HVSII Sequence Variation of Altaian Haplogroup X mtDNAs

		RFLP Haplotype[a]	HVSI, HVSII Sequence[b]
		111	111111
		1046	666666
		7345	11112201122333
		1961	88892775916001
		5457	23933833553995
Sample	Origin	ccse	a aba
CRS		+−−−	AAT−CCAATAA——
ALT16	Northern Altaians	−.++	CCCCTTGGCGGCCC
ALT43	Northern Altaians	−.++	CCC.TTGGC.G..C
ALT81	Southern Altaians	−.++	CCCCTTGGC.GCCC
ALT161	Southern Altaians	−.++	CCC.TTGGC.GCCC
ALT171	Southern Altaians	−.++	CCC.TTGGC.GCCC
ALT188	Southern Altaians	−.++	CCC.TTGGC.GCCC
ALT208	Southern Altaians	−.++	CCC.TTGGC.GCCC

[a] Restriction-endonuclease sites are indicated as follows: c = *Dde*I, e = *Hae*III, s = *Acc*I. A dot (.) denotes identity with the Cambridge reference sequence (Anderson et al. 1981); a plus sign (+), which denotes a site gain, or a minus sign (−), which denotes a site loss, indicates deviation from the CRS.

[b] HVSI (nucleotide positions 15991–16400) and HVSII (nucleotide positions 20–420) were sequenced. A dot (.) indicates identity with the CRS, and a dash (—) indicates nucleotide insertion.

may have come to the Americas via a Eurasian migration. The virtual absence of haplogroup X in eastern and northern Asia raises the possibility that some American Indian founders were of European ancestry. In that case, as it has been proposed, haplogroup X was brought to America by the eastward migration of an ancestral white population, of which no trace has so far been found in the mtDNA gene pool of modern Siberian/eastern Asian populations (Brown et al. 1998).

However, it should be stressed that mtDNA-variability studies of the populations living in this major geographic area were performed on a limited number of populations. Some regions remain poorly sampled, and more extensive sampling is required. Moreover, some key markers, including those defining the X-haplogroup sequences, have not been typed for many different populations. These limitations do not allow correct definition of the phylogenetic status of mtDNA lineages.

To extend the survey of Asian mtDNAs for the presence of haplogroup X, we screened the mtDNAs of a total of 790 individuals for the RFLP markers (−1715 *Dde*I, −10394 *Dde*I, +14465 *Acc*I, and +16517 *Hae*III) that define this lineage. These individuals comprised 10 aboriginal Siberian populations: Buryats ($n = 105$), Tuvinians ($n = 111$), Koryaks ($n = 35$), Evens ($n = 65$), Yakuts ($n = 62$), Khakassians ($n = 54$), Shors ($n = 42$), Sojots ($n = 34$), Altaians ($n = 202$), and Evenks ($n = 80$). All individuals belonged to the indigenous population of the regions studied, were unrelated, and stated that their maternal grandmother had been born in the area considered for this study.

Haplogroup X mtDNAs were detected only in Altaians, at a frequency of 3.5%. The haplogroup X status of these haplotypes was confirmed through HVSI and HVSII mtDNA sequencing (table 1). All Altaian X mtDNAs harbored the consensus haplogroup X motif: −1715 *Dde*I, +14465 *Acc*I, +16517 *Hae*III, 16189C, 16223T, 16278T, 73G, 153G, 195C, 263G, relative to the Cambridge reference sequence (Anderson et al. 1981) and differed from each other by length-polymorphism mutations at nucleotide positions 16193, 309, and 315. One of these X mtDNAs (ALT16) also harbored a 215G variant (table 1) that has not been observed in either American Indian or European X haplotypes. It should also be noted that none of the Altaian X mtDNAs harbored the 225A variant, which is a marker for a major part of haplogroup X (Brown et al. 1998).

Analysis of published data on European HVSI and HVSII mtDNA sequences (Piercy et al. 1993; Calafell et al. 1996; Torroni et al. 1996; Brown et al. 1998; Lutz et al. 1998; Parson et al. 1998; Rousselet and Mangin 1998; Helgason et al. 2000) demonstrates that the overwhelming majority of X haplotypes (23 of 25 X sequences) harbor the 225A variant. In contrast, the X haplotypes without 225A have been observed mostly in American Indians (11 of 14 Ojibwa; see table 1 in Brown et al. 1998). Nevertheless, the X mtDNAs that we detected in the Altaian sample do not bear the 16213A and 200G variants that are characteristic of most American Indian haplogroup X mtDNAs (Brown et al. 1998).

Figure 1 illustrates the reduced median network, constructed by means of the median algorithm of Bandelt et al. (1995), encompassing the HVSI and HVSII variation observed in the American Indian, European, and Altaian haplogroup X mtDNAs. The network suggests that European and American Indian haplogroup X mtDNAs are separated into two major branches, whereas the majority of Altaian X mtDNAs appear to be very similar to the root of haplogroup X phylogeny, differing from it by one step (loss of 225A). The network further suggests that the Altaian X haplotypes occupy the intermediate position between European and American Indian haplogroup X mtDNA lineages (fig. 1).

The Altaians, the native people of Altai Republic (south Siberia) number up to 60,000 persons. "Altaians" is the common denomination for seven formerly distinct Turkic-speaking groups: the Altai-Kizhi, Teleuts, and Telenghits, who are southern Altaians, and the Chelkans, Kumandins, Tubalars, and Maimalars, who are northern Altaians. The differences between southern and northern Altaians are well established, on the basis of anthropological, linguistic, and classical genetic-marker studies (Potapov 1969; Alexeev and Gohman 1984; Luzina 1987). Anthropologically, southern Altaians are typical

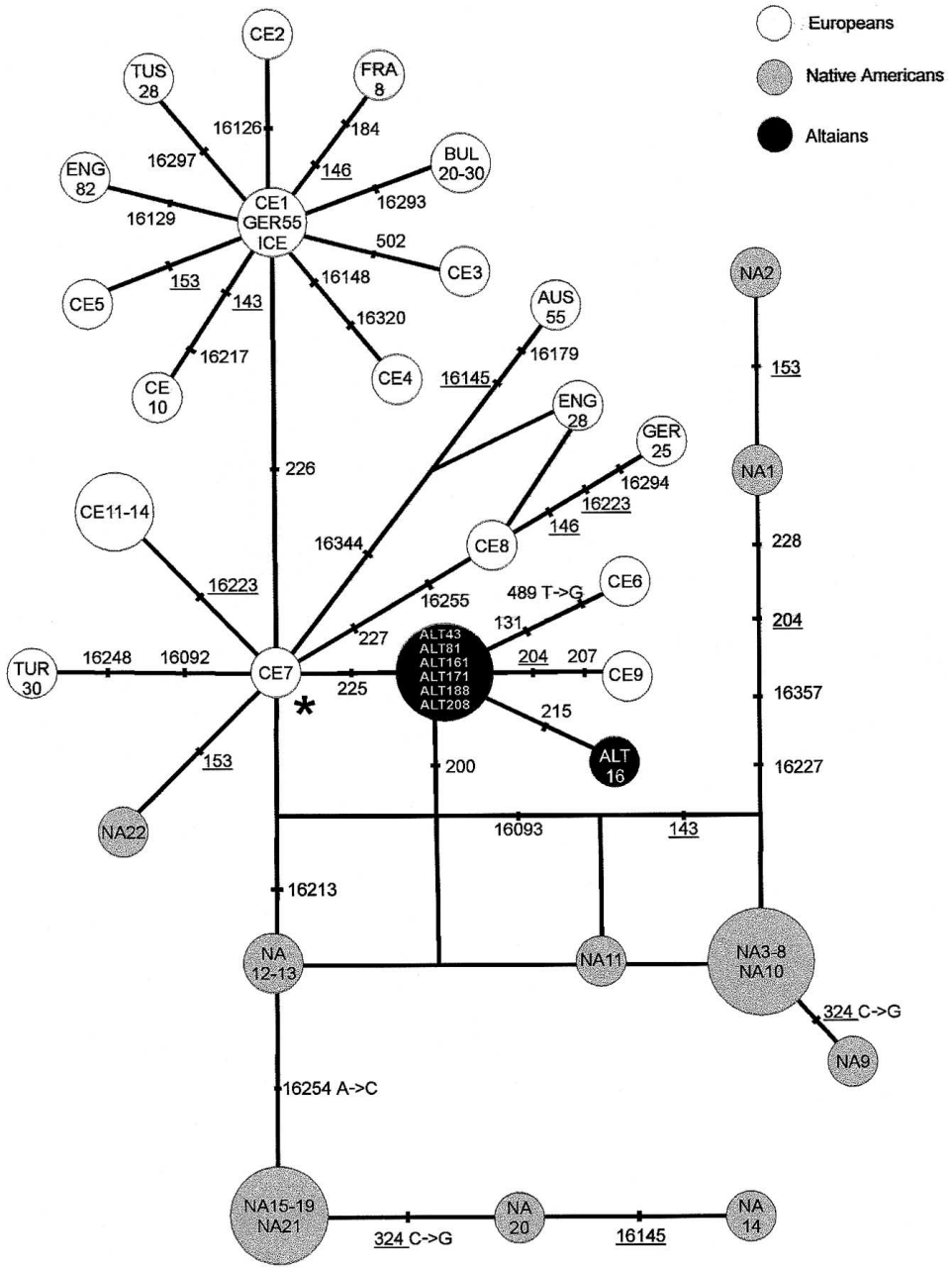

Figure 1 Reduced median network of haplogroup X mtDNAs, as defined by HVSI and HVSII variation. RFLP status of the sequences is known for American Indians (NA; Brown et al. 1998); for Altaians (ALT) from the present study; and for some Europeans (CE; Brown et al. 1998). The other European sequences—GER (Lutz et al. 1998), ENG (Piercy et al. 1993), TUS (Torroni et al. 1996), FRA (Rousselet and Mangin 1998), BUL and TUR (Calafell et al. 1996), AUS (Parson et al. 1998), and ICE (Helgason et al. 2000)—were assumed, on the basis of their HVSI and HVSII sequences, to belong to haplogroup X. Sample origin is indicated by the scheme (see key). mtDNA types are represented by circles, with areas proportional to number of individuals. Lines are labeled by HVSI and HVSII mutations. Nucleotide variants correspond to transitions, whereas transversions are further specified. The insertions/deletions, as well as variations of C's in the unstable regions between nucleotide positions 16182–16193 and 309–315 were not included. The node marked with an asterisk (*) matches the haplogroup X basic motif: −1715c, +14465s, 16189C, 16223T, 16278T, +16517e/16519C, 153A, 195C, and 225A. The restriction site changes indicated by their enzyme letter code listed in table 1. Underlining indicates nucleotide positions that have mutated more than once, and reticulations indicate ambiguity in the topology. Parallel lines in a reticulation represent the same mutation.

central Asian Mongoloids (like Mongolians, Yakuts, and Buryats), whereas northern Altaians exhibit some Caucasoid anthropological features, similar to those of Ugric and Samoyedic groups.

The Altai region was populated during the Lower Paleolithic, and there is ample evidence of settlement during the Middle Paleolithic. It was proposed by anthropologists that, at least from the Neolithic, the territories of Altai and Sayan region were populated by mixed tribes with Caucasoid and Mongoloid anthropological features, but later they were replaced by Mongoloid populations of central Asian origin (Alexeev and Gohman 1984). The analysis of the tribal structure of Southern Altaians has shown that the present-day Altaians have retained their native language and ethnic identity. They have begun to mix with other ethnic groups (mostly Russians and Kazakhs) only recently, so the interethnic admixture is estimated to be <5% (Luzina 1987; Osipova et al. 1997). The haplogroup X mtDNAs have not been found in populations of central Asia, including Kazakhs, Uighurs, and Kirghizs (Comas et al. 1998). Since the frequency of haplogroup X in Russians is extremely low (3 of 336; Orekhov et al. 1999; Malyarchuk and Derenko 2000; authors' unpublished data), the recent European admixture cannot explain the presence of haplogroup X in the Altaians. Hence, the results of the present study allow us to suggest that haplogroup X was the part of the ancestral gene pool for Altaian populations, being found both in northern and southern Altaians.

Recently, the mtDNA studies have shown that both northern and southern Altaians exhibit all four Asian and American Indian–specific haplogroups (A–D) with frequencies of 57.2% (Sukernik et al. 1996) and 46.8% (Derenko et al. 2000*a*), respectively, exceeding those reported previously for Mongolians, Chinese, and Tibetans. Therefore, they may represent the populations which are most closely related to New World indigenous groups. Since the detection of all four haplogroups (A–D) in an Asian population is thought to be a first criterion in the identification of a possible New World founder, the candidate source population for American Indian mtDNA haplotypes therefore may include the populations originating in the regions to the southwest and southeast of Lake Baikal, including the Altai Mountain region (Derenko et al. 2000*b*). The presence of X mtDNAs in Altaians is generally consonant with the latter conclusion.

Because the location and identification of the population that was the source of the founding lineages for the New World is a question of considerable interest, several studies on Y-chromosomal DNA polymorphism were performed recently to investigate Pleistocene male migrations to the American continent (Underhill et al. 1996; Lell et al. 1997; Karafet et al. 1999; Santos et al. 1999). It has been shown that the major Y haplotype present in most American Indians could be traced back to recent ancestors they have in common with Siberians: namely, the Kets and Altaians, from the Yenisey River Basin and the Altai Mountains, respectively (Santos et al. 1999). Similarly, based on a comprehensive analysis of worldwide Y-chromosome variation, it has been proposed that populations occupying the general area including Lake Baikal (eastward to the Trans-Baikal and southward into Northern Mongolia), the Lena River headwaters, the Angara and Yenisey River basins, the Altai Mountain foothills, and the region south of the Sayan Mountains (including Tuva and western Mongolia) was the source for dispersals of New World Y-chromosome founders (Karafet et al. 1999). It is obvious that we have now the genetic evidence that will allow closer determination of which Siberian population was the source of the population expansion leading to modern American Indians and will allow relation of the studies of migrations from Siberia to the Americas that are based on paternally inherited genetic systems with those based on maternally inherited ones.

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