Letters to the Editor

Am. J. Hum. Genet. 70:1376–1377, 2002

Revised 14.7-cM Locus for the Hyperparathyroidism–Jaw Tumor Syndrome Gene, *HRPT2*

To the Editor:

We reported previously that the locus for hyperparathyroidism–jaw tumor syndrome (MIM 145001), *HRPT2,* appeared to be within a 0.7-cM region on chromosome 1q, on the basis of shared haplotype data from two families (Hobbs et al. 1999). The map order of the markers was originally derived from the chromosome 1 maps from Généthon (Dib et al. 1996; Généthon Web site) and the Whitehead Institute for Genome Research (Whitehead Institute for Genome Research Web site). Recent work by Carpten et al. (2000) and the human genome sequencing project (Lander et al. 2001) have shed new light on the proposed locus. These detailed physical-map data change the order of two markers (underlined) that are important in defining the shared haplotype region (in parentheses), from (D1S466, D1S2701, CHLC.12F10, D1S240, D1S2848, D1S254), D1S191, D1S444 to (D1S466, D1S2701, CHLC.12F10, D1S240, D1S254), D1S444, D1S191, D1S2848 (centromeric to telomeric). This removes D1S2848 from the reported shared haplotype region. Telomeric to D1S240, a new marker also became available: 277P67-2A8 (GenBank accession number AF181675). This marker was not shared between the two families in question, further reducing the shared haplotype region to the area defined between D1S466 and D1S240 (~1.8 cM): (D1S466, D1S2701, CHLC.12F10, D1S240), 277P67-2A8, D1S254, D1S444, D1S191, D1S2848.

For the markers remaining in the shared haplotype region—D1S466, D1S2701, CHLC.12F10, and D1S240—the frequencies for the alleles found in the affected haplotype are 0.06, 0.74, 0.18, and 0.50, respectively. This gives a calculated frequency in the general population of 0.004, or 1/250. This haplotype is much more common than that calculated for the original proposed shared haplotype region (population frequency of 1/38,000) and indicates that the newly reduced shared haplotype region is not indicative of an *HRPT2* haplotype.

Furthermore, the reduced shared haplotype region (D1S466 to D1S240) now no longer overlaps with the nonrecombinant region for our families (277P67-2A8 to D1S306, or D1S477 in current databases [Human Genome Working Draft Web site]). We conclude that the *HRPT2* gene must lie within this 14.7-cM nonrecombinant region. Although our initial shared haplotype data provided misleading results, the examination of shared haplotype data in different families has proven valuable in refining the map location for other disease gene loci (i.e., the loci for autosomal dominant Stargardt-like macular dystrophy [Donoso et al. 2001] and primary erythermalgia [Drenth et al. 2001]) and should continue to be explored in uncommon genetic diseases.

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Electronic-Database Information

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

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for marker 277P6-2A8 [accession number AF181675])
Généthon, http://www.genethon.fr/

Human Genome Working Draft, http://genome.ucsc.edu/ (for the sequence from D1S240 to D1S477, estimated at 17.5 Mb)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for hyperparathyroidism–jaw tumor syndrome [MIM 145001])
Whitehead Institute for Genome Research, http://www-genome.wi.mit.edu/

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The Peopling of the Americas: A Second Major Migration?

To the Editor:

Recently, Lell et al. (2002) analyzed the distribution of Y-chromosome haplogroups in a set of Siberian and Native American individuals. They inferred that there is evidence of two major migrations that originated from Siberia and peopled the Western Hemisphere. The first one coincides with our previous finding (Santos et al. 1999) and that of Karafet et al. (1999). In addition, Lell et al. (2002) suggest that a later major migration, which likely originated in eastern Siberia, would have carried the haplogroups S4Y (as previously suggested by Karafet at al. [1999]) and M45b. We argue that the claim of a second major migration is not well grounded and is altogether not necessary to explain the distribution of the haplogroups S4Y and M45b in Native American populations.

On the basis of detailed molecular information associated with the most common Native American M3 haplogroup and its immediately ancestral M45a haplogroup, Santos et al. (1999), Karafet et al. (1999), and Lell et al. (2002) have consistently identified central Siberia as the most likely region of origin of the present-day Native American Y chromosomes. We suppose that, when this "first" major migration occurred, the central Siberian population was polymorphic, like most if not all human populations. Natural populations usually contain few common alleles and several rare ones, but only a subset of the total rare alleles will be represented in a sample of, for example, 10–50 individuals (Ewens 1972; Helgason et al. 2000). When a population movement occurs, migrants reflect (more or less) the distribution of the source population. Therefore, we expect that most migrants carry common alleles but also that some of them carry rare ones. The first settlement of the Americas has been associated with a probable bottleneck event (Wallace et al. 1985; Pena et al. 1995; Bonatto and Salzano 1997*b;* Santos et al. 1999). It could have produced drastic changes in allele frequencies and reduced the number of rare alleles; however, even if this were the case, it does not mean that the genetic variability completely disappeared. The ancient haplogroup S4Y has a wide and heterogeneous distribution in eastern Asia. In central Siberia, the putative region of the "first" migration, its frequencies are 2/12 in Kets, 2/122 in Selkups (Karafet et al. 1999), 13/40 in Tuvan, 2/19 in Tofalars, and 18/31 in Yenisey Evenks (Lell et al. 2002). Among the 31 Native American populations in which the presence of the haplogroup S4Y has been tested, only four samples exhibit this allele—always at low frequencies (1%, 16%, and 7%)—and only one sample of 12 Tanana individuals from North America presents five S4Y chromosomes (95% CI 12%–62%). Therefore, it is clear that the S4Y haplogroup is a rare allele in Native American populations. Since we have no reason to believe that the individuals carrying the haplogroup S4Y were prohibited from migrating at the time of the first settlement of the continent, we do not think that it is necessary to claim an *ex novo* major migration to explain the presence of this haplogroup at low frequencies

in Native American populations. Instead, the most parsimonious explanation for its presence in the American indigenous population seems to be that it entered as a rare allele during the first settlement of the continent.

Indigenous samples from Central and North America have low frequencies of the haplogroups S4Y and M45b. On the other hand, eastern Siberian samples coincidentally show the higher frequencies of the haplogroups S4Y and M45b (even if the latter is altogether a rare allele). Lell et al. (2002) present this observation as evidence that a second major migration originated in eastern Siberia. Actually, these populations exhibit frequencies of the S4Y haplogroup that are 40%–100%. Under the two-major-migrations model, the Native American population would be an admixed population with two parental ones: (1) the central Middle Siberian and (2) the Lower Amur/Okhotsk populations. We used the classical Bernstein formula (Cavalli-Sforza and Bodmer 1971) to calculate the contribution of each putative parental population to the current gene pool of Native American populations. The S4Y haplogroup could be useful for this purpose because it has the highest difference in allele frequencies among the parental population ($\delta = 0.45$) and is not affected by recent European or African migration. Using the data presented by Karafet et al. (1999) and Lell et al. (2002), we considered as parental populations the central southern Siberia region (Yenisey Evenk, Tuvan, Tofalar, Buryat, Ket, and Selkup samples were clumped) and the Lower Amur/Okhotsk region (Okhotsk, Ulchi, Negidal Upp, Negidal Low, Udigey, Nivkh, Buriat, Siberian Evenk, Even, Manchurian Evenk, Oroquen, and Yakut samples were clumped). The calculated contribution of the Lower Amur/Okhotsk population to the current gene pool of the Native American population would be −26% (a negative value, because the frequency in the Native American population is lower than that in central southern Siberia). Although this is a rough measure of admixture, subject to a high stochastic variance, it illustrates that the proposal of a second major migration, even intuitively, is hardly compatible with current data. The obtained value is clearly more compatible with a null contribution of the Lower Amur/Okhotsk population. Again, we do not need to claim a second major migration to explain the variability of Native American Y chromosomes. When its wide distribution is considered, the haplogroup S4Y seems to be very ancient (Karafet et al. 1999; Underhill et al. 2000), and its presence in central southern Siberia at the time of first migration to the Americas is also compatible with current data. Furthermore, although Lell et al. (2002, p. 204) state that their data "demonstrate that the Native American RPS4Y-T haplogroup originated in the eastern Siberian populations," we were not able to find that demonstration in the article. Because the authors do not disclose to the public the complete information about the frequencies and distribution of S4Y-microsatellite haplotypes, we are not able to discuss this point. However, we anticipate that the above pending demonstration must include an adequate assessment of its statistical significance.

Lell et al. (2002) suggest that the distribution of 22 Y chromosomes belonging to the rare haplogroup M45b also supports the existence of the second major migration from eastern Siberia. According to Lell et al. (2002), the 17 M45b chromosomes observed in the Americas would have an eastern Siberian origin. We have an alternative explanation for the origin of a consistent portion of the 17 M45b chromosomes found in the Americas, which is—we think—simpler and perhaps obvious: Since the M45b haplogroup is largely the most frequent in virtually all western European populations (Semino et al. 2000), these chromosomes could have been introduced into Native American populations by Europeans during the last five centuries. In fact, evidence of European admixture in Native American populations, especially in North and Central America, is straightforward and comes from population-genetics, demographic, and historical studies (see Crawford [1998], Salzano and Callegari-Jacques [1988], and the second principal component of Amerindian genetic variability shown by Cavalli-Sforza et al. [1994]). Furthermore, several genetic studies have shown that European admixture in the Americas has been preferentially mediated by males (Merriwether et al. 1997; Carvajal-Carmona et al. 2000; Carvalho-Silva et al. 2001). Therefore, in populations in which evidence of admixture exists, like the Seminole or the Boruca (14%; Sans 2000), we should expect to find some level of European Y-chromosome contribution, as is clearly evidenced by previous studies (Pena et al. 1995; Santos et al. 1995, 1996*b;* Bianchi et al. 1997; Karafet et al. 1999; Ruiz-Linares et al. 1999). For instance, our group has previously demonstrated that the most common European Y-chromosome haplotype (defined by the alleles αh-II and DYS19-B), which we refer to as "II-B" (Santos et al. 1996*a*) and which is equivalent to M45b (data not shown), is present at higher frequencies in Native American populations such as the Muskokes of North America, who have a long documented history of contact and admixture with Europeans (Santos et al. 1996*b*). Curiously, even though Wallace's group has previously reported in the Seminole sample the presence of 11% of Y chromosomes with likely European origin (Huoponen et al. 1997), in the Lell et al. (2002) article they ignore this possibility but consider the eventuality of male African admixture, which is generally less likely than European admixture. Furthermore, in accordance with their probable recent European origin, the microsatellite haplotypes found by Lell et al. (2002) in the M45b chromosomes match very well with those present in the phylogenetically equiva-

lent haplogroup 1 chromosomes of Basques, Catalans, Norwegians, French, and Italians (Hurles et al. 1999; Ruiz-Linares et al. 1999; Carvajal-Carmona et al. 2000; Rosser et al. 2001). Therefore, if we consider that a consistent portion of the 16 M45b chromosomes found in North and Central America very likely arrived during the last five centuries and that only 6 M45b chromosomes were found in eastern Siberia, very few chromosomes are left for making any robust inference about the genetic structure of populations or "major migrations." In any case, in Siberian populations, the association claimed by Lell et al. (2002) between central and eastern Siberia and the distribution of M45a and M45b haplogroups is far from reaching any acceptable significance level (Fisher exact test: $P = .25$), which means that any derived conclusion, such as the eastern Siberian origin of the Native American M45b chromosomes, is at least temerarious. Perhaps the only valid observation we can make is that the M45b haplogroup is a rare one either in native populations of northeastern Asia or in the Americas.

We think that Lell et al. (2002) have not provided any solid evidence about the existence of a second "major migration," and we think that the simplest way to reconcile the currently available molecular genetic data, which are mainly derived from Y chromosomes and mtDNA (Bonatto and Salzano 1997*a,* 1997*b*), is to assume a single major migration from Siberia contributing to the gene pool of Native American populations.

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Reply to Tarazona-Santos and Santos

To the Editor:

Tarazona-Santos and Santos (2002 [in this issue]) make two arguments against our proposal that there was a second Y-chromosome migration from the Amur River/Sea of Okhotsk region of eastern Siberia that contributed to northern Native American populations. Their first argument is that the S4Y Y-chromosome lineage found in northern Native Americans may have been derived from central Siberia, rather than from eastern Siberia, as we proposed. There are several reasons why an eastern Siberian origin for S4Y Y chromosomes is much more likely than a central Siberian origin. First, a broad survey of Asian Y chromosomes has indicated that S4Y was brought to Siberia from Southeast Asia, primarily via a coastal migration (Su et al. 2000). Consistent with this assertion, there is very limited S4Y Y-chromosomal variation in central Siberia, which is best explained by recent admixture, rather than an ancient origin. For example, the limited number of S4Y Y chromosomes reported by Karafat et al. (1999) in the Selkups and Kets were most likely derived from the recent expansion of the Evenks from the Lake Baikal region of eastern Siberia into the Lower and Middle Yenisey River region (Tugolukov 1985). Similarly, the Tuvan, which are currently dispersed in the extreme south of Siberia, were most likely derived from the greater Manchuria homeland of Altaic speakers, which includes the Lower Amur River Basin. Indeed, nomadic Altaic speakers had occupied Tuva long after the migration bringing the S4Y chromosome to the Americas took place (Janhunen 1996). Finally, the current average S4Y Y-chromosome frequency in North American is likely to be much lower than the S4Y Y-chromosome frequency in the original second migration, simply because these Y chromosomes would have been diluted by the predominant M3 Y chromosomes already in residence from the first Native American migration. Given these facts, Tarazona-Santos and Santos's Bernstein admixture calculation does not provide a compelling argument against a second migration.

Tarazona-Santos and Santos's second argument is that the M45b Y-chromosome haplotypes that we identified in northern Native Americans are not Siberian in origin, but European. However, this argument would require that the proposed European male input into the Native American populations not only was extensive but also brought only a limited number of Y-chromosome haplotypes—specifically, those with the microsatellite alleles DYS19(11 repeats)-DYS388(11 repeats)-DYS390(11 repeats)-DYS391(10 or 11 repeats). This possibility is contrary to the historical fact that European male admixture into Native American populations has been continuous over the past 500 years and that it has been derived from populations throughout western Europe. By contrast, the M45b Y-chromosome microsatellite markers that we found in northern North Americans are either identical to or closely related to those that we found in eastern Siberia. Hence, we feel that it is much more likely that the M45b Y chromosomes, which are common in northern Native Americans, came from the Siberian Pacific,

where the remnants of their exact counterparts are currently located.

Any hypothesis is subject to question and, with compelling data, should be revised. Therefore, we appreciate Tarazona-Santos and Santos's thoughts on this matter. Indeed, we also initially considered a possible European origin for the M45b Y chromosomes in northern Native Americans. However, after careful analysis of the existing data, we concluded that a two-Siberian-migration hypothesis for the origin of Native American Y chromosomes provided the most reasonable explanation for the available observations.

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Increased Rate of Twins among Affected Sibling Pairs with Autism

To the Editor:

There is consistent evidence from twin and family studies implicating genetic factors in the etiology of autism (MIM 209850), but no specific genes associated with autism have yet been identified. In a recent article in the *Journal,* Greenberg et al. (2001) reported a striking excess of twin pairs, both MZ and DZ, in the cohort of families with at least two siblings with autism or autism-related conditions recruited by the Autism Resource Exchange (AGRE) of the Cure Autism Now (CAN) Foundation. The proportion of twins among autistic sib pairs (18%, 30/166) was significantly higher than the expected twinning rate per sib pair (2.4%). Greenberg et al. (2001) demonstrated that to ascribe this excess of twins with autism to a sampling bias would require very large ascertainment factors, which seem unlikely. These findings suggest that being a twin represents a risk factor for autism, and they have important implications for the etiology of autism. However, as Greenberg et al. (2001) pointed out, these results need to be replicated in other data sets. We report here a similar excess of twins in a sample of affected sib pairs recruited by the Paris Autism Research International Sibpair (PARIS) study.

Families with two or more children with autism or autism-related disorders (Asperger syndrome or pervasive developmental disorder not otherwise specified [PDD NOS]) were recruited by the PARIS study at specialized clinical centers in eight countries (Austria, Belgium, France, Israel, Italy, Norway, Sweden, and the United States). Patients were included after undergoing a complete clinical and neuropsychological assessment described elsewhere (Philippe et al. 1999); subjects demonstrated to suffer from organic conditions associated with autism, such as tuberous sclerosis, fragile X syndrome, or other established chromosomal disorders, were excluded from the study. We divided the affected sib pairs into two diagnostic categories: "narrow," when both affected sibs had autism, and "broad," when one or both of the affected sibs had either Asperger syndrome or PDD NOS. Patients in the narrow diagnostic category fulfilled the DSM-IV and ICD-10 criteria for autistic disorder/childhood autism and met the Autism Diagnostic Interview–Revised algorithm (Lord et al. 1994). All the families were white except one of mixed ethnicity (white/Asian).

To make our results directly comparable to those ob-

Table 1

Distribution of Affected Sib Pairs

GROUP	NO. IN DIAGNOSTIC CATEGORY[a]		
	Narrow	Broad	Total
Singletons	59 (34, 23, 2)	9 (5, 4, 0)	68 (39, 27, 2)
DZ twins	2 (2, 0, 0)	0	2 (2, 0, 0)
MZ twins	9 (7, —, 2)	0	9 (7, —, 2)
Total	70 (43, 23, 4)	9 (5, 4, 0)	79 (48, 27, 4)

[a] Numbers in parentheses indicate breakdown into male-male, mixed sex, and female-female pairs, respectively.

Table 2

Observed Proportion of Twins Compared with Population Rates and with Results of the Study by Greenberg et al. (2001)

		Greenberg et al. (2001)[a]		Narrow Diagnosis		Narrow + Broad Diagnoses	
Twin Group	Population Rate[b]	Rate Observed	P[c]	Rate Observed	P[c]	Rate Observed	P[c]
DZ	.016	.072 (12/166)	<.00005	.029 (2/70)	N.S.	.025 (2/79)	N.S.
MZ	.008	.102 (17/166)	<.000001	.129 (9/70)	<.000001	.114 (9/79)	<.000001
All	.024	.181 (30/166)	<.000001	.157 (11/70)	<.000001	.139 (11/79)	<.000005

[a] Includes narrow + broad diagnoses.
[b] From Greenberg et al. (2001).
[c] Two-sided, exact binomial calculations. N.S. = not significant.

tained by Greenberg et al. (2001), in the current analysis we included only families having exactly two affected offspring; families with triplets or with an affected twin pair and one or more affected nontwin siblings were excluded. We also excluded families with mixed twin pairs (one affected twin, one unaffected co-twin, and a nontwin affected sib) and families with half siblings.

Table 1 shows the distribution of affected sib pairs divided according to diagnostic category, twin status, and sex. Table 2 shows the observed proportion of twins in our data set compared both with the population rates reported by Greenberg et al. (2001) and with the rate observed in the AGRE families. In agreement with the results of Greenberg et al. (2001), we observed a remarkably high proportion of MZ twin pairs among affected sib pairs. Of 79 affected sib pairs (narrow + broad diagnoses), 11 were twin pairs (2 DZ and 9 MZ). This represents a 14-fold increase for MZ twins, compared with the population frequency, and is statistically significant ($P < 10^{-5}$). In contrast, we did not observe a significant increase in the proportion of DZ twins.

We did not include the following families in the calculations: (1) one family with affected triplets (two MZ and one DZ); (2) one family with two affected MZ twins plus an affected nontwin; (3) one family with two affected twins (zygosity unknown) plus two affected nontwins; (4) one family with one affected MZ twin, one co-twin deceased during the first year of life, and a nontwin affected sib; and (5) three sets of discordant DZ twins (one affected and one unaffected). Together with the other twin pairs, these families further reinforce the hypothesis that twinning per se is a significant risk factor for autism.

The high proportion of twins among affected sib pairs with autism observed by Greenberg et al. (2001) and replicated in our data set strongly suggests the involvement of biological factors rather than an ascertainment bias. Moreover, different ascertainment methods were used in our study and that of Greenberg et al. (2001): the AGRE families were recruited exclusively via mailings and presentations to autism support groups, whereas the majority of our families were collected by clinicians members of the PARIS study among their clinic cases.

The PARIS study collects affected sib pairs for linkage studies but also parent-offspring trios for association studies. We do not preferentially collect MZ twins, but neither do we turn them away, because these families can be analyzed in association studies. In our data set, only MZ twins were overrepresented among affected sib pairs. Although Greenberg et al. (2001) observed an excess of both DZ and MZ twins among their families, the deviation from population rates was more important among MZ twins (12-fold) than among DZ twins (4-fold). As mentioned by Greenberg et al. (2001), the excess of MZ twins compared with DZ twins in autism suggests that the estimates of heritability based on concordance for autism in MZ pairs versus DZ pairs may be overestimated. These intriguing findings also emphasize the need to explore the participation of nongenetic as well as genetic factors in the etiology of autism.

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Electronic-Database Information

The accession number and URL for data in this letter are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for autism [MIM 209850])

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