2005

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Keywords
genes, time, space, origins

Disciplines
Anthropology | Genetics | Social and Behavioral Sciences

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Over the past several decades, researchers have obtained considerable genetic data from Native American and Siberian populations for the purpose of elucidating the nature and timing of the peopling of the New World. Most of these studies have shown a genetic linkage between populations from northern Asia and the Americas. However, because of using different molecular markers, not all of them have presented the same picture of biological variation in these populations. At the same time, comparing the colonization models generated from different genetic data sets has yielded new insights into the genetic relationships between Siberian and Native American groups. This paper provides a brief historical overview of these biogenetic studies, and also discusses the ways in which future research may further illuminate our understanding of the colonization of the Americas.

Introduction

As evident from the numerous papers presented in this volume, the colonization of the New World is an anthropological issue that is still being vigorously debated. All the earliest inquiries and much of the current research into this question have focused on the linguistic, archaeological, and osteological evidence from northern Asia and the Americas, with various models of the colonization process being proposed to explain the patterns of variation seen in these data sets. These models provided certain temporal benchmarks against which subsequent research results could be measured, and predicted population relationships that could be tested against new empirically derived associations.

In the mid-1960s, researchers began using biochemical methods to analyze molecular variation in Siberian and Native American populations, primarily protein polymorphisms such as red cell enzymes, serum proteins, and blood group markers. With these protein polymorphism data, they were able to define biological relationships among aboriginal populations of Siberia and the Americas in novel ways. New quantitative methods developed to deal with population genetic data further refined the assessment of population variation and structure, particularly issues such as effective population sizes, founder effects, and mutation rates. However, protein variants provide an indirect picture of the actual genetic variation in human populations because they are the products encoded by genes, not the gene sequences themselves. Hence, the underlying mutations responsible for these polymorphisms remained unknown.

With the advent of new technologies to assess genetic variation at the DNA sequence level, it became possible to determine the underlying genetic variants responsible for the known protein polymorphisms. These advances also expanded the number and types of genetic loci that could be analyzed in human evolutionary studies. A number of these loci encoded proteins involved in normal physiological or immunological functions of the body, such as the hemoglobin, HLA, and immunoglobulin genes. Because of their functional importance, the distribution of the alleles present at these loci appears to have been strongly influenced by selective forces, along with the usual population genetic forces such as drift, gene flow, and mutation.

An enormous boost for human genetic studies came in the mid-1980s with the invention of the polymerase chain reaction (PCR). With this method, researchers could enzymatically amplify specific regions of genes, or even whole gene sequences, a million-fold or more, thereby generating an abundance of DNA for use in various genetic studies, something that was previously

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possible only through the more involved process of molecular cloning. The PCR further permitted the analysis of genetic markers and genes that were formerly difficult to characterize, as well as the large-scale screening of population samples for these markers in far less time than required to conduct assays of classical genetic markers.

These trends were greatly enhanced in the last decade by the development of new technologies to assess genetic variation. Among these developments were automated sequencing methods for rapidly characterizing gene sequences, and computational methods for ascertaining population relationships and genetic substructure of populations. In addition, studies associated with the Human Genome Project (HGP) revealed whole new classes of genetic markers in different regions of the sex chromosomes and autosomes that could be used for population genetic studies. These markers included restriction site polymorphisms (RSPs), short tandem repeat (STR) polymorphisms, and single nucleotide polymorphisms (SNPs), most of which are effectively neutral in their overall genetic effects. The current and rapidly expanding genetic database of molecular markers pertinent to anthropological genetic studies is a direct reflection of these developments. These technological advances have further permitted the identification of the molecular mutations that create the protein polymorphisms in the classical genetic systems (e.g., blood group markers, serum proteins, erythrocyte enzymes, HLA and immunoglobulin alleles) that were previously used in population genetic studies.

In the following pages, I discuss a number of the major genetic systems that have been employed in studies of the peopling of the Americas over the past several decades. Although briefly considered because of space constraints, fuller explanations of the nature of these genetic systems and the mechanisms that generate polymorphisms in them can be found in the cited papers and references appearing therein. This group of genetic systems is by no means an exhaustive compilation, but does represent the primary set that has been utilized for most population genetic studies. It includes uniparentally and biparentally inherited markers, rapidly and slowly evolving genomes, and functional and non-functional loci. Together, they provide a comparative framework in which to evaluate the genetic diversity of Native American populations and its implications for the peopling of the New World. As will become apparent, these new molecular data have allowed researchers to re-examine colonization models based on archaeological, linguistic, osteological, and anatomical evidence, as well as test models of population relationships based on published protein polymorphism and nuclear genetic data sets.

Classical Protein Polymorphisms

The earliest studies of non-osteological biological affinities of Native Americans focused on the blood group antigen, serum protein, and erythrocyte enzyme variation in these populations. Blood group markers, or antigens, are proteins and glycoproteins located on the cell membranes of erythrocytes (red blood cells) (Avent 1997; King 1994). These antigens further represent five functional categories, including transporters and channels, receptors for exogenous ligands, adhesion molecules, enzymes, and structural proteins (Avent 1997; Cartron et al. 1998; King 1994). Many of them were initially discovered in transfusion experiments directed towards understanding immunogenetic complementation between mothers and their offspring or blood donors and recipients, and are also medically important in treating autoimmune anemia and in organ transplants (Avent and Reid 2000; Reid and Yazdanbakhsh 1998; Suto et al. 2000). A number of the macromolecules that confer blood group antigenicity are also receptors for pathogenic organisms, and as a result these pathogens may have played a role in the evolution of blood group polymorphisms (e.g., the Duffy glycoprotein [a chemokine receptor] and the malarial parasite *Plasmodium vivax*) (Daniels 1997; Hamblin and Di Rienzo 2000). At present, a total of 23 different blood groups markers have been identified on erythrocytes. Some of the more commonly known markers include the ABO, Rhesus (RH), and Duffy (Df) systems, with the majority of these having recently been molecularly characterized and cloned (e.g., ABO system, Yamamato et al. 1990; RH system, Ikemoto et al. 1996). Based on these studies, most blood group polymorphisms are caused by missense mutations that produce amino acid substitutions, but some are generated through gene deletion, single base deletion, or recombination (Daniels 1997).

Serum proteins and erythrocyte enzymes perform different but no less important physiological functions in the body. Among other functions, they are involved in the immune response (Langlois and Delanghe 1996), iron metabolism (Brock et al. 1986; Rouault and Klausner 1997), antioxidant protection (Krsek-Staples and Webster 1993; Langlois and Delanghe 1996), lymphocyte proliferation (Brock et al. 1986; Rouault and Klausner 1997), cellular differentiation (Moriwaki et al. 1999), glycogen metabolism (Whitehouse et al. 1998), adenine homeostasis (Nakazawa et al. 1990), and the elimination of immune complexes (Volanakis 1990). As a consequence, mutations in the genes coding these polypeptides can lead to serious biochemical diseases, particularly those affecting normal erythrocyte function. Erythrocytes themselves generate high-energy adenosine triphosphate (ATP) by anaerobic glycolysis, as well as cycle oxidized and reduced nicotinamide adenine dinucleotide phosphate (NADP) through the aerobic pentose phosphate shunt pathway (Valentine et al. 1985). Mutations that produce defects in the erythrocyte enzymes involved in the pentose phosphate shunt typically cause hemolysis resulting from the oxidative denaturation of hemoglobin, while those affecting enzymes participating in anaerobic glycolysis cause hemolytic anemia (Valentine et al. 1985). An example of one of these enzymopathies is glucose-6-phosphate (G-6-P) deficiency, which is known to be clinically, biochemically, and molecularly heterogeneous across the world. G-6-P catalyzes the first step in the pentose phosphate pathway, and generates NADPH to protect erythrocytes against oxidizing agents and in reductive biosynthesis reactions (Au et al. 2000; Notaro et al. 2000).

A large number of other erythrocyte enzyme loci have been analyzed for variation in Siberian and Native American popula-

tions. In addition to G-6-P, other loci include adenylate kinase (AK) phosphoglucomutase (PGM), carbonic anhydrase II (CAII), peptide hydrolase (PEP), 6-phosphogluconate dehydrogenase (6-PGD), adenosine deaminase (ADA), acid phosphatase (AcP), esterase D (EsD), glyoxalase (GLO), cholinesterase-2 (CHE2), and galactose-1-phosphate uridyltransferase (GALT). Quite a few serum protein loci have also been surveyed for genetic variation, including haptoglobin (Hp), transferrin (Tf), group-specific component (Gc), human complement component C3 (CO3), ceruloplasmin (Cp), and albumin (Al). Because so many of these protein loci have been studied in Native American and Siberian populations over the past three decades, it is impossible to adequately summarize all of the patterns of variation that have been observed at each of these loci in these populations. However, one can provide a general overview of the results and implications of these studies as they pertain to the peopling of the New World, which follows below.

In the 1960s and 1970s, researchers conducted a large number of studies of variation at these classical protein polymorphism loci in Native Americans (e.g., Barrantes et al. 1990; Mestriner et al. 1976, 1980; Mohrenweiser et al. 1979; Neel 1973, 1978, 1980; Neel, Gershowitz et al. 1977; Neel, Tanis et al. 1977; Neel et al. 1980; Salzano et al. 1972; Salzano, Gershowitz et al. 1977; Salzano, Neel et al. 1977; Salzano et al. 1980; Salzano and Callegari-Jacques 1980; Spielman et al. 1979; Tanis et al. 1973, 1977). These studies provided numerous insights into the population diversity and structure of unacculturated native populations. Many of them revealed a number of unique alleles, or "private polymorphisms," at different genetic loci in various populations in Central and South America. Private polymorphisms appear to have arisen after the colonization of the New World, and apparently reflect the influences of selection, genetic drift, or isolation on many of these populations since their initial settlement in various regions of the Americas. The continued discovery of these kinds of variants at the same genetic loci in newly characterized Native American populations, especially those from South America (e.g., Dipierri et al. 1998; Luiselli et al. 2000), confirms these trends. Furthermore, these studies indicated that the biological diversity in South American Indians resulted from a process of fission-fusion model of village propagation, one which led to the isolation of subpopulations and their subsequent genetic differentiation, with limited local gene flow occurring thereafter (Neel 1980; Salzano et al. 1980; Sokal et al. 1986; Ward et al. 1975).

Initial studies of classical protein markers in North American Indians revealed pronounced north-south clines in markers frequencies (Suarez et al. 1985). In particular, Eskimo populations appeared to be genetically distinct from Amerindians on the basis of lower ABO*O and higher BO*B frequencies (Suarez et al. 1985). There was also evidence of the association of allele frequencies and the linguistic affiliations of these populations (Spuhler 1979), and the possible geographic patterning of these traits (O'Rourke et al. 1985; Spuhler 1979; Suarez et al. 1985). These allelic distributions were further interpreted as showing the effects of natural selection operating in different ecological zones, as well as the influences of migration and admixture (O'Rourke et al. 1985; Suarez et al. 1985).

Looking more broadly across the New World, there was somewhat greater genetic heterogeneity among South Amerindians compared with North Amerindians, with Central Amerindians being much less diverse than either one of them (O'Rourke and Suarez 1986; O'Rourke et al. 1992). O'Rourke et al. (1992) also found no evidence of north-south clines for specific erythrocyte antigen alleles in or geographic structuring of allelic distributions in South American Indians. They attributed this pattern to the stochastic effects of genetic drift in geographically isolated populations. However, Salzano and Callegari-Jacques (1988) observed significant north-south clines for blood group markers, and found that these data separated South American populations into three major groups: Tropical Forest, Paleo-American, and Andean language groups. Salzano et al. (1991) and Callegari-Jacques et al. (1994) also noted differences between tribes living north and south of the Amazon River, suggesting this river might have constituted a barrier to north-south gene flow. These apparent discrepancies could also reflect differences in the number of genetic markers and the number of populations used in the two studies.

There were also substantial differences in genetic structure in North, Central, and South Amerindian populations. Both North and Central American populations showed evidence of isolation by distance, whereas South American groups did not (O'Rourke et al. 1992). This difference was attributed to low migration among South American groups. Low migration rates could have produced the extreme differentiation between adjacent groups because genetic drift shapes allele frequencies such that geographically separated, unrelated groups appear to be more similar than they actually are. On the other hand, O'Rourke et al. (1992) found little evidence that migration had been attenuated in these populations, as the genetic data revealed considerable proto-historical migrations within the continent.

Compared with North and South American groups, Central Amerindians were much less diverse (O'Rourke et al. 1992). In fact, the Central American pattern of gene-geographic relationships was intermediate between North and South America, but more similar to that seen in North America. Barrantes et al. (1990) also observed geographic structuring of erythrocyte allele frequency data in Central America, and attributed this pattern to the linguistic diversity of the region. It was also hypothesized that the geographic constriction in Central America, as well as increased population density and differentiation in Central America, may have resulted in blockage of population movement southward from North America (Barrantes et al. 1990; O'Rourke et al. 1992). As a result, genetic drift operating in small migrant groups present in South America before later population movement from Central America may have contributed to the spatial heterogeneity of genetic traits in the southern continent.

Other trends in population associations emerged through the analysis of data from circumarctic populations. Analyzing a variety of erythrocyte and serum protein markers in Alaskan and

Siberian Eskimos, Crawford et al. (1981) and Ferrell et al. (1981) showed a good fit between the genetic structure, geographic distribution, linguistic affiliation (Yupik versus Inupik), and ethnohistory of these populations. Similarly, differences between the Yupik, Inupik, and the Koniaq Eskimos and Aleuts were observed by Crawford and Enciso (1982) and Majumder et al. (1988). Crawford and Enciso (1982) further noted some separation between Coast and Reindeer Chukchi populations, with the former being closer to Eskimo and Aleut populations and the former showing a certain closeness to Nganasans and other Samoyedic-speaking populations.

Comparable differences between Na-Dené (Athapaskan) Indians and Eskimo-Aleuts were noted by Scott (1979) and Harper (1980) in their analysis of protein polymorphism data. Based on these data, Harper (1980) proposed that ancestral Native Americans (Amerindians) originated around 19,000 yr B.P. and entered the New World about this time. Na-Dené Indians, and the Bering Sea Mongoloids from which Eskimo-Aleut populations evolved, diverged somewhat later, around 15,000 yr B.P., with the Bering Sea Mongoloids emerging as a distinct entity at roughly 10,200 yr B.P. In addition, using genetic information and archaeological data from Alaska and the Aleutian Islands, Harper (1980) suggested that the Eskimos and Aleuts diverged around 9000 yr B.P., with the Inupiaq and Yupik-speaking Eskimo populations splitting around 5000 yr B.P..

Among northeast Siberian populations, the Chukchi and the Asiatic Eskimos showed significant allelic heterogeneity in blood group marker and serum protein distributions among their constituent subgroups, as well as between them (Sukernik et al. 1981). These findings supported the interpretation that genetic drift had played an essential role in shaping the genetic variation of Siberian and circumarctic peoples (Sukernik et al. 1981). They further suggested that northeastern Siberian populations have lived relatively isolated from one another, despite greater contact between different groups in historical times, with each experiencing a relatively unique genetic history since they began inhabiting this region.

This general pattern was also observed in later studies of native Siberian populations. One analysis of blood group markers and serum protein polymorphisms revealed clusters of eastern Siberian groups that reflected their geographic location or linguistic affiliation (Dubrova et al. 1993). These clusters included Turkic-, Mongolic-, Tungusic-, and Chukotko-Kamchatkan-speaking populations, with members of the latter cluster including Reindeer and Coast Chukchi and Siberian Eskimos. A similar analysis of classical protein polymorphisms in native populations from west, central, and eastern Siberia showed the same overall trends but also more complex relationships among these groups (Posukh et al. 1998). Eastern Siberian (Tungusic/Yukagir) and Samoyedic populations formed distinct clusters, with Nganasans showing similarities to eastern Siberian groups. In addition, northwestern native populations (Komi, Nentsi, Entsi) and ethnic Russians formed a grouping. In contrast, Altaic populations were equidistantly separated from all these clusters and showed affinities with Mongol groups, largely due to their having considerable frequencies of both European and Asian genetic markers (Posukh et al. 1998). These data suggested that the distribution of genetic markers among these partially isolated indigenous populations have been primarily shaped by genetic drift effects and gene flow, and to some extent by local and regional events in their recent history.

HLA Genes

Many aspects of Native American origins and affinities have been elucidated through the characterization of variants of the major histocompatibility locus antigen (HLA) system. The HLA system is the most polymorphic genetic system in humans, and has been extensively typed in numerous world populations (e.g., Bodmer et al. 1998). This system is highly polymorphic because balancing selection maintains a few allelic lines over very long periods of time (Harpending et al. 1998; Hedrick and Black 1997; Watkins et al. 1992). The great variation in its genetic markers also makes the HLA system very useful for determining genealogical relationships between populations.

HLA antigens belong to three classes based on their immunological properties, two of which have been frequently used in studies of human biological variation. Class I proteins, which are found on every mammalian cell, are called the transplantation antigens, since they are responsible for accepting or rejecting foreign tissue. The human class I proteins include the classical transplantation antigens HLA-A, -B, and -C (Bodmer et al. 1998; Browning and McMichael 1996). By contrast, class II proteins, which are found on the surfaces of B and T lymphocytes and macrophages, facilitate communications between cells that are involved in executing the immune response. The human class II region is arranged into four subregions: DR, DQ, DZ/DO, and DP (Bodmer et al. 1998; Browning and McMichael 1996). Recent molecular typing methodologies have permitted the further definition of subtypes within both class I and II genes, leading to the development of a new nomenclature for HLA variants that differs from the one based on immunocomplementation and protein electrophoresis (Bodmer et al. 1998).

Some general trends in the pattern of HLA variation in Native American populations have been seen in these studies. To begin with, Native American populations exhibit an overall reduction of the number of HLA alleles relative to other non-Amerindian populations. However, the same alleles and allelic lineages were missing in a number of Amerindian groups, suggesting that they shared a common set of HLA allotypes (Erlich et al. 1997). The occurrence of a number of unique alleles in various populations in the Americas also suggested that they have arisen since the colonization of the Americas, much like the "private polymorphisms" in blood group marker and serum protein systems in South American Indian populations. Together, these data suggested that the First Americans experienced a population bottleneck as they entered the New World (Erlich et al. 1997).

There was also evidence of larger-scale population dynamics within the American continents. For example, Rothhammer et al. (1997) studied HLA-A, -B, and -C types from 39 South American Indian populations and observed significant longitude and latitude clines in allele frequencies, which were viewed as reflecting ancient migration patterns through that continent. Similarly,

Black (1991) noted some geographic structuring of HLA alleles in South American Indian groups, and attributed this pattern to recent population histories, linguistic affiliations, or genetic drift effects. On the other hand, in a comparison of Venezuelan and Brazil tribes, Layrisse et al. (1995) noted a closer relationship between two linguistically but geographically distant Venezuelan tribes, the Bari and the Warao, compared with two culturally different Brazilian populations. Therefore, while language and geography have influenced the distributions of HLA-A, -B and -C alleles, they are not absolute predictors of genetic relationships between different South American Indian groups.

In addition, various studies have indicated that the HLA-B locus has evolved much more rapidly in Central and South American Indian populations than in North American tribes. For example, Iwanaga et al. (1997) detected the presence of new HLA-B alleles in the Kuna of Panama, Marcos et al. (1999) noted a variety of new HLA-B* alleles and some new HLA-A alleles in Argentinean and Brazilian Amerindian populations, Martinez-Laso et al. (1996) observed new HLA-B alleles in the Venezuelan Bari, and Watkins et al. (1992) detected several new HLA-B alleles in the Brazilian Waorani. In contrast, the Navajo had limited HLA-B diversity comparable to other North American Amerindian tribes (Garber et al. 1996), and the Zuni were noted to have HLA-A and -B alleles that were also present in Asian populations (Watkins et al. 1992). These data have been interpreted as showing that South American populations have been under considerable selection pressure for increased allelic diversity (Erlich et al. 1997; Watkins et al. 1992).

Among HLA class II genes, the DRB1 locus has been most widely surveyed in Native American populations. Most studies of this locus indicate that Native American populations have a reduced number of alleles relative to non-Amerindian groups (Cerna et al. 1993; Erlich et al. 1997; Monsalve et al. 1998; Yunis et al. 1994). The same appears to be true for the DQA1 locus, as two alleles were common among the Navajo, Pueblo, and Sioux Indian groups (Scholl et al. 1996) and in two Alaskan native populations (Walkinshaw et al. 1996). As for HLA class I loci, there is also evidence of the emergence of Amerindian-specific alleles from the ancient DRB lineage (Erlich et al. 1997). For instance, Mack and Erlich (1998) found several new variants within the Brazilian Ticuna, including the new DRB1*0807 allele, Cerna et al. (1993) found the unique DRB1*0417 in the Brazilian Xavante, Layrisse et al. (1997) found the DRB1*0807 allele in the Venezuelan Yucpa, and Lozáro et al. (1999) found a number of novel alleles in the Brazilian Terena. Similarly, Erlich et al. (1997) identified new DRB1 alleles in several Amerindian groups from Brazil, Argentina, Ecuador and Canada. These results again point towards selection driving the creation of new HLA class II alleles, with most evidence indicating a functionally significant, more rapid evolution of class I compared with class II loci (e.g., Lozáro et al. 1999).

Based on combinations of these new molecular variants at class I loci, Monsalve et al. (1999) observed several major HLA haplotypes in Native American populations. One was common to Amerindian populations, including the Northwest Coast Salishans (Monsalve et al. 1999). The second was present at high frequencies in Athapaskans (Monsalve et al. 1998), occurred in a few Amerindian groups (Williams et al. 1994), and appeared in some eastern Siberian and East Asian populations (Grahovac et al. 1998). The third was common in both Salishan and Amerindian populations, as well as other Asian groups (Monsalve et al. 1999), whereas the fourth occurred at modest frequencies in Northwest Coast Indians (Monsalve et al. 1999) and northeast Asian populations (Grahovac et al. 1998). These data clearly showed the genetic links between North-East Asians and Native Americans and, in revealing specific patterns of haplotype sharing amongst these same populations, suggested genetic differences among Native American populations (Eskimo-Aleut, Na-Dené Indians, Amerindians).

Monsalve et al. (1999) also used a maximum-likelihood analysis to examine the phylogenetic relationships among HLA class II loci data from Native American and Asian populations (Cerna et al. 1993; Gao et al. 1991; Grahovac et al. 1998; Imanishi et al. 1992; Layrisse et al. 1995; Lozáro et al. 1999; Mack and Erlich 1998; Monsalve et al. 1998, 1999; Trachtenberg et al. 1996; Yunis et al. 1994). This analysis revealed that Northwest Coast Indians and Na-Dené Indians grouped together outside of the main Amerindian branch, and were intermediate between Asians and Amerindians. In addition, South American Indian groups generally clustered together away from North and Central American Indian groups. Eastern Siberian populations clustered together and formed a larger branch with central Siberians (Evenks, Kets), but were separated from East Asian populations. Monsalve et al. (1999) also noted greater interpopulational differences in Amerindian populations relative to Asian groups, probably because of the effects of genetic drift, which played a major role in shaping allelic distribution. Furthermore, geographic proximity was a major factor in the clustering of specific populations, as was linguistic affiliation to a lesser extent.

Variations in class II loci have also been examined in Siberian populations. One analysis of DRB1, DQA1, DQB1, DPA1 and DPB1 loci revealed a number of interesting features in seven central and eastern Siberian populations (Grahovac et al. 1998). While there was high polymorphism at most loci, no new alleles were detected. However, this high polymorphism generated numerous class II haplotypes, more than observed in other world populations. Some of these were shared with other non-Siberian groups but most were unique to these Siberian populations and, in some cases, represented novel combinations of DQA1 and DQB1 alleles. These data led Grahovac et al. (1998) to suggest that the colonizers of Siberia brought with them a set of haplotypes common to Eurasian populations that have since undergone extensive recombination to form these new haplotypes, ones which are still rapidly turning over. In addition, the allele frequencies at the DRB1 locus divided eastern and central Siberian populations, with the former showing clear genealogical relationships to Native Americans, a pattern also seen by Krylov et al. (1995).

Immunoglobulin Genes

The elucidation of genetic relationships among Native American tribal groups with immunoglobulin genes has also allowed

the testing of hypotheses concerning their ancestry. Immunoglobulin proteins are antibodies secreted into the blood by the B-lymphocytes (B cells) in response to the presence of an antigen. Each immunoglobulin molecule comprises a tetramer of two identical light (L) chains and two identical heavy (H) chains, the combination of which generates an immunoglobulin with several discrete domains. Each individual protein chain consists of two principal regions, the variable (V) and constant (C) regions. The variable domain of the light chain (VL) is responsible for recognizing the antigen, with the production of various VL domains of differing specificities creating the ability to respond to diverse antigens. Accordingly, the total number of variable regions for both the light and heavy chains number in the hundreds (Alexander et al. 1985; Marchalonis and Schluter 1989; Sitnikiva and Su 1998). In addition, different classes of immunoglobulins have different effector functions, the class of which is determined by the heavy chain C region. Immunological responsiveness is maintained through the somatic recombination of the V, C, and joining-segment gene segment in B-lymphocytes (Alexander et al. 1985; Marchalonis and Schluter 1989; Sitnikiva and Su 1998). Because of their integral role in the human immune function, immunoglobulin genes have likely been under some form of selection during the expansion of modern humans into the Eurasia and the Americas.

The immunoglobulin data from Williams et al. (1985) were initially viewed as best supporting the tripartite migration hypothesis of Greenberg et al. (1986). This study showed three distinct sets of GM allotypes among Amerindians (GM*A G [GM1;21] and GM*X G [GM1,2;21]), Na-Dené Indians (GM*A G, GM*X G, and GM*A T [GM1,2;21]), and Aleut-Eskimos (GM*A G and GM*A T). Although there was a very large standard error estimated with the genetic distances on which this model was based, the Na-Dené Indians grouped closer to Eskimos and Chukchi than to Amerindians. However, Szathmary (1993) asserted that this data set actually shows Eskimos to have GM*X G allotype irrespective of admixture with other groups, and questioned whether the Eskimos were clearly demarcated from Na-Dené Indians and Amerindians with this genetic system.

Subsequent analyses of GM allotype data in Native American populations led to a further refinement of the tripartite migration model (Schanfield 1992; Schanfield et al. 1990). These analyses detected four main groupings of Native Americans, Eskimo-Aleuts, Na-Dené Indians, North and Central Amerindians, and South Amerindians, although these divisions were not entirely unambiguous. In addition, the Inupiaq Eskimos clustered closer to Yupik Eskimos and Canadian Athapaskans, and then to the Chukchi, whereas Alaskan Athapaskans clustered with Uralic-speaking Siberians (Schanfield et al. 1990). Both studies also suggested that the northern Asian haplotype GM*A T was polymorphic only in Eskaleut, Na-Dené Indians, and some northern Amerindian groups, being seen only sporadically in other Amerindian groups, although this interpretation was not universally accepted (Szathmary 1993).

These patterns led to the proposal that four separate migrations to the New World were responsible for the pattern of GM variation present in these aboriginal groups (Schanfield et al. (1990); Schanfield (1992). The first migration brought only GM*A G and GM*X G haplotypes, as reflected by the data from South American Indians (Black and Pandey 1997; Dugoujon et al. 1995; Schanfield 1992). The second migration to enter North America had high frequencies of GM*A G, and low frequencies of GM*X G and GM*A T, as seen in North and Central Amerindians. The third migration, represented by Na-Dené Indians, had high frequencies of GM*A G, and moderate frequencies of GM*X G and GM*A T, whereas the fourth, represented by Eskimo-Aleuts, had only GM*A G and GM*A T. These results were generally supported by a later analysis of GM variation in around 50 different Native American populations, which revealed a strong north-south gradient in GM allotypes frequencies from the Bering Strait to South America (Dugoujon et al. 1995), and the distinctiveness of Eskimos and Na-Dené Indians compared to other Amerindian groups.

Similar studies of nuclear genetic variation in aboriginal populations of Siberia and northern North America revealed close genetic relationships among certain northern Asian and Native American groups. To begin with, the GM*A G, GM*X G, and GM*A T allotypes were present in most eastern Siberian and East Asian populations (Crawford and Enciso 1982; Dubrova et al. 1993; Posukh et al. 1990, 1998; Schanfield et al. 1980, 1990; Sukernik et al. 1978, 1981). Hence, the major GM haplotypes present in Native American groups are widespread through Northern Asia. In particular, the GM*A T haplotype variant was observed among the Chukchi, Eskimos, Na-Dené Indians, and northern Amerindian populations of North America, suggesting a common origin for this haplotype among circumarctic populations, as well as the occurrence of gene flow between Na-Dené Indians and northern Amerindians. In addition, "private polymorphisms" and "lineal effects"observed in Native American groups (Neel 1980) were also detected in the Sel'kups and Forest Nentsy of western Siberian lowlands, including unique tribal-specific GM haplotypes such as IG1G-deleted, which varied significantly in frequency within their tribal boundaries (Sukernik et al. 1992). Furthermore, the population structure and genetic variation of the Forest Nentsy, Sel'kups, Nganasans, Yukagirs, Evens, Chukchi, and Siberian Eskimos also implied that aboriginal populations had undergone substantial genetic differentiation prior to their subsequent expansion into new environments (Sukernik et al. 1980, 1981, 1986a, b, 1992).

Synthetic Maps of Multiple Genetic Loci

The analysis of multiple nuclear genetic loci in Native American and Asian populations showed some of the same associations revealed in more focused studies of blood group marker or HLA loci variation, but also some intriguing discrepancies with them. These studies used allele frequency data from multiple nuclear genetic loci from many populations to estimate genetic distances between them, and then employed phylogenetic or principal components analysis to ascertain the evolutionary relationships

amongst them. In one such analysis of 60-plus loci, Cavalli-Sforza et al. (1994) observed that Athapaskan Indians and North American Eskimos clustered together on the same branch but were not closely related to each other, and both were clearly separated from other Amerindian populations. In addition, North American Indian populations grouped together at some distance from those in the U.S. Southwest and Central America. There was also some clustering of Central and South American tribes along geographic lines, as well as some mixing of groups across linguistic boundaries.

Looking more broadly in the circumarctic region, Cavalli-Sforza et al. (1994) noted several distinct patterns of population relationships across the Bering Strait. The Siberian Eskimos grouped with the Coast Chukchi and Koryaks in a single branch that was positioned some distance from their North American counterparts. Even more interesting was the separation of Reindeer and Coastal Chukchi populations, and the association of the former population with the Mongols of southeastern Siberia. Thus, this analysis revealed splits among linguistically related populations such as the Siberian and Alaskan Yupik Eskimos, divisions within the same ethnic population, as in the case of the Reindeer and Maritime Chukchi, as well as associations between groups that had previously been seen in other genetic and non-genetic data sets (e.g., Na-Dené Indian closeness to Alaskan Eskimos).

The analysis of Asian and Siberian populations was equally as informative (Cavalli-Sforza et al. 1994). The results revealed a small cluster that encompassed northeastern Siberians, including the Koryaks, Chukchi, Tungus (Evens), and a North Turkic grouping (Yakuts, Tuvans, Altayans, Dolgans). There was also a northern mongoloid subcluster containing East Asian and northeastern Siberian populations, within which Bhutanese, Tibetans, northern Han Chinese, Koreans, and Japanese grouped together, then Mongols and Uralic Siberians, then Reindeer Chukchi. Principal components mapping of these allele frequencies showed roughly the same patterns of population associations: Eurasian (West and South Asia), Northeast and East Asia, and Southeast Asia. Within these general groupings were clusters containing Mongols, Ainu, Koreans, Japanese; (2) Tibetans, northern Tungus, northern Han Chinese; (3) Nentsy, Samoyed, Nganasan and, surprisingly, Reindeer Chukchi. When Arctic populations were considered alone, some of these population associations changed. The Eskimos clustered with Na-Dené Indians; Uralic-speaking groups clustered together; the Lapps (Saami) formed a small distinct cluster, as did northwestern Siberian (non-Russian) groups; and all central, northeastern, and southeastern Siberia groups clustered together.

In their analysis of multiple nuclear genetic loci, Nei and Roychoudhury (1993) observed somewhat different sets of population relationships among Native American and Asian populations. Native Americans clustered together away from a greater Asian cluster, with northeast Asians being closest to New World populations. In addition, North American Indians were separated from South American Indian populations, and both of these groups appeared distinct from Eskimos. The Eskimos were also positioned closer to North American Indians than South American groups. These differences in population clustering may reflect the use of different statistical and tree-building methods used by Nei and Roychoudhury (1993) and Cavalli-Sforza et al. (1994).

Alu Polymorphisms

The pattern of variation observed in Native Americans with polymorphic Alu insertions was somewhat different than for other genetic systems. Alu elements belong to the largest family of short interspersed repetitive elements (SINEs) in humans, with over 500,000 copies being present in each haploid genome (Batzer et al. 1991, 1996). While distributed throughout the genome of primate species, one Alu subfamily has been found to be largely human specific, having been inserted into the genome of the human lineage between 200,000 and 6,000,000 years ago (Batzer and Deininger 1991; Batzer et al. 1996). A minority of these are transcriptionally active (Matera et al. 1990) and undergo amplification, or retroposition, into other genomic locations (Wallace et al. 1991). Most Alu insertions are stable once situated in the genome because there is no mechanism for removing them, except for intrachromosomal deletion. In addition, because of the low rate of *de novo* insertions reaching polymorphic levels (Batzer and Deininger 1991; Batzer et al. 1991), the likelihood of the same insertion occurring in the same place more than once is extremely small. Therefore, the ancestral state of an Alu element is its absence at a particular position (-), with the derived state being its presence (+). It follows from this general pattern that Alu elements are inherited by offspring from parents through the simple Mendelian segregation of codominant + and - alleles (Novick et al. 1995).

Using a set of five Alu elements from different chromosomes, Novick et al. (1998) screened 24 native populations from North, Central, and South America for these markers. Their results supported an Asian origin of ancestral Native American populations, but not a multiple-migration hypothesis for the emergence of Eskimo-Aleuts, Na-Dené and Amerind linguistic groups. Instead, these data were interpreted as supporting a single migration to the New World followed by partial isolation and genetic drift. Based on heterozygosity values for these Alu loci, Novick et al. (1998) also noted the mixing of some North, Central, and South American populations apparently in both north-to-south and south-to-north directions. There was also a deficiency of heterozygotes in Native American populations. This finding likely reflected the variable degree of inbreeding in these populations or the lack of gene flow among them.

Interestingly, the maximum likelihood (ML) analysis of genetic distances generated from Alu haplotype data did not reveal clusters of Native American populations that conformed to the linguistic groupings of Greenberg et al. (1986). Instead, the clusters in the ML tree generally reflected the geographic location of the populations. However, a few tribal groups were positioned with geographically distant populations, such as the South American Wayuu with the North American Sioux, the South American Inca with the Greenland Eskimos, and the North American

Navajo and Zuni with the South American Karitiana. These anomalies were attributed to non-native admixture causing deviations from expected branching patterns based on known cultural and linguistic affiliations (Novick et al. 1998). While noting these apparent discrepancies, Novick et al. (1998) suggested that this pattern of genetic variation in the Americas was produced by a single migration to the New World followed by partial isolation and genetic drift. They further noted a close phylogenetic relationship between mainland Han Chinese and Native Americans, particularly the Mayans, and suggested possible recent gene flow from China to the New World.

Mitochondrial DNA

Much of the more recent molecular research into the colonization of the New World has employed the mitochondrial DNA (mtDNA). The human mtDNA has a number of distinct properties that make it an invaluable tool for molecular anthropological studies, including its maternal inheritance (Case and Wallace 1981; Giles et al. 1980), rapid mutation rate (Brown et al. 1979; Horai et al. 1995; Miyata et al. 1982; Stoneking et al. 1986; Wallace et al. 1987), and lack of recombination (Clayton 2000; Merriwether et al. 1991; Shadel and Clayton 1998). Because of these properties, one can reconstruct patterns of accumulated sequence changes in mtDNAs along branching female lineages with relatively minimal ambiguity. Furthermore, many of the mutations detected in human mtDNAs correlate with the geographic origin of the population in which they occur (e.g., Ballinger et al. 1992; Chen et al. 1995, 2000; Torroni et al. 1996, 1998; Torroni, Lott et al. 1994). This mutational pattern may provide a detailed record of ancient migration patterns based on their distribution in human populations, since the presence of specific mutations in groups distantly located likely reflects population movement or contacts in prehistoric times. Finally, being a haploid genome, the mtDNA is very sensitive to stochastic processes such as genetic drift and founder effects that result from geographic isolation, migration, or population splits (Livshits and Nei 1990; Nei 1987; Nei and Livshits 1989). For this reason, variation in mtDNA sequences often contains genetic signals of these past events.

Studies of mtDNA variation in modern Native American populations have shown that their mtDNAs belong to five different haplogroups, or mtDNA lineages, of related genotypes, which have been designated A–D and X (Bailliet et al. 1994; Batista et al. 1995; Brown et al. 1998; Easton et al. 1996; Forster et al. 1996; Ginther et al. 1993; Horai et al. 1993; Kolman et al. 1995; Kolman and Bermingham 1997; Lorenz and Smith 1996, 1997; Merriwether et al. 1994, 1995; Santos et al. 1994; Santos et al. 1996; Schurr et al. 1990; Smith et al. 1999; Torroni et al. 1992; Torroni, Chen, et al. 1994; Torroni, Neel, et al. 1994; Torroni, Schurr, et al. 1993; Ward et al. 1991, 1993, 1996). These findings have been substantiated by the results of similar analyses of ancient Native American populations (Fox 1996; Hayes 1999; Kaestle 1995, 1997; Merriwether et al. 1994; Monsalve et al. 1996; O'Rourke et al. 2000; Parr et al. 1996; Ribeiro-Dos-Santos et al. 1996; Stone and Stoneking 1998). Thus, the presence of five distinct haplogroups in the New World is no longer in question. In addition, some of these studies detected the presence of "Other" (non-haplogroup A–D) haplotypes in different Native American groups (Bailliet et al. 1994; Lorenz and Smith 1996; Merriwether et al. 1994, 1995; Ribeiro-Dos-Santos et al. 1996; Smith et al. 1999; Torroni, Schurr et al. 1993; Ward et al. 1991). The presence of "Other" haplotypes in Native Americans was significant because they could potentially represent previously unidentified founding mtDNA lineages that were brought to the New World during its initial phase of colonization. On the other hand, these haplotypes could reflect the occurrence of non-native admixture in Native American populations that has occurred in a post-Columbian context. Thus, the definition of these kinds of haplotypes was critical for resolving the number of founding lineages that were brought to the Americas.

One possible founding mtDNA lineage was observed among South American Indians in the form of "X6/X7" haplotypes (Easton et al. 1996; Merriwether et al. 1994, 1995). X6/X7 haplotypes had the +DdeI 10394 and +AluI 10397 sites (DdeI/AluI sites) seen in haplogroup M, a macrolineage that encompasses 55–70 percent of all Asian mtDNAs (Ballinger et al. 1992; Torroni, Miller, et al. 1994; Torroni, Schurr et al. 1993), but otherwise lacked the diagnostic RFLPs of haplogroups C and D, while differing between themselves by the presence or absence of the HaeIII 16517 site. Based on their mutational properties, and because putatively similar mtDNAs were identified in other Native American populations (Merriwether et al. 1994, 1995; Torroni, Schurr et al. 1993), X6/X7 haplotypes were proposed to represent an additional founding lineage of Asian origin (Easton et al. 1996; Merriwether et al. 1994, 1995). However, when the CR sequences of X6/X7 mtDNAs were analyzed with those from other Native American populations, they clustered among Amerindian CR sequences from haplogroups C and D (Schurr 1998; Schurr and Wallace 1999; Stone and Stoneking 1998). These results suggested that X6/X7 mtDNAs were autochthonous haplotypes that derived from haplogroup C and D mtDNAs after the peopling of the Americas rather than haplotypes belonging to an additional founding lineage.

The great majority of the remaining "Other" mtDNAs were likely acquired through historical non-native gene flow. Several studies have revealed slight but non-negligible European admixture in North American Indian groups by the presence of haplogroups H, J, and K (Scozzari et al. 1997; Smith et al. 1999; Torroni, Schurr et al. 1993). With further RFLP marker screenings, additional North American populations with "Other" mtDNAs may also exhibit the same kinds of haplotypes. These studies have also revealed the presence of African mtDNAs in Native American populations (Huoponen et al. 1997; Smith et al. 1999; Torroni, Chen, et al. 1994c). African haplotypes have also been found in admixed populations of North, Central, and South America, such as Black Caribs (Monsalve and Hagelberg 1997), Cubans (Torroni et al. 1995), Mexican-Americans (Green et al. 2000), and Afro-Brazilian and Afro-Uruguayan populations (Bortolini et al. 1997; Bravi et al. 1999). Because most of these admixed populations also possess Amerindian mtDNAs, they

may be thought of as reservoirs of Native American genes belonging to groups that no longer exist as distinct tribal entities.

Even after eliminating haplotypes originating in African or European populations, some "Other" mtDNAs in Native American populations have not yet been assigned to a known haplogroup. Most of these "Other" mtDNAs were identified in ancient populations (e.g., Hauswirth et al. 1994; Parr et al. 1996; Ribiero-dos-Santos et al. 1996), with a minority being detected in modern populations (Bailliet et al. 1994). However, none of these "Other" mtDNAs were screened for the RFLP markers defining haplogroups M or X. Furthermore, in most cases, the portion of the CR region that was sequenced in ancient samples was not of comparable length to that typically obtained from modern samples. As a result, the limited data from these samples make it impossible to know exactly what their genealogical status actually is.

The accumulation of genetic data from a large number of Native American populations from all continental regions has revealed that mtDNA haplogroups are differentially distributed in Americas. While haplogroups A–D are found throughout the Americas (Bailliet et al. 1994; Batista et al. 1995; Brown et al. 1998; Easton et al. 1996; Forster et al. 1996; Ginther et al. 1993; Horai et al. 1993; Kolman et al. 1995, 1997; Lorenz and Smith 1996, 1997; Merriwether et al. 1994, 1995; Santos et al. 1994; Santos et al. 1996; Schurr et al. 1990; Smith et al. 1999; Torroni et al. 1992; Torroni, Chen, et al. 1994; Torroni, Neel, et al. 1994; Torroni, Schurr, et al. 1993; Ward et al. 1991, 1993, 1996), haplogroup X seems to be confined to North America (Brown et al. 1998). In addition, haplogroup A appears at high frequencies in North and Central America, but diminishes in frequency in South America, whereas haplogroups C and D appear at roughly inverse frequencies in the New World. By contrast, haplogroup B occurs at fairly similar frequencies in the Americas, although appearing at high frequencies in the American Southwest. Whether this pattern reflects the consequences of multiple colonization events, or instead the process of settlement and regional differentiation of a single ancestral population, is still being explored. However, it has apparently been stable over many thousands of years, at least in North America (O'Rourke et al. 2000).

These studies have further shown that all circumarctic populations have predominantly haplogroup A and D mtDNAs (Saillard et al. 2000; Schurr et al. 1999; Shields et al. 1993; Starikovskaya et al. 1998; Torroni, Schurr, et al. 1993; Ward et al. 1991, 1993). Amongst these populations, the Siberian and Alaskan Eskimos appeared genetically very similar to one another by having higher frequencies of haplogroup A, while the Aleuts differed from Eskimo groups by having mostly haplogroup D mtDNAs (Hayes 1999; Saillard et al. 2000; Schurr, et al. 1993; Schurr et al. 1999; Shields et al. 1993; Starikovskaya et al. 1998; Torroni, Merriwether et al. 1994; Ward et al. 1991, 1993). In addition, both sets of Eskimo groups had a very low frequency of haplogroup C mtDNAs. This finding suggested that haplogroup C could represent a founding mtDNA lineage in Eskimo-Aleut populations, although those in the Siberian Eskimos may have been obtained through gene flow with the Chukchi (Schurr et al. 1999; Starikovskaya et al. 1998). On the other hand, known gene flow from Europeans (Russians) into the Alaskan Eskimos and Aleuts, and from the Chukchi into the St. Lawrence Eskimos (Crawford et al. 1981; Ferrell et al. 1981), as well as tribal interactions with Northwest Coast Amerindian populations (Szathmary 1993), make it likely that the very low frequencies of haplogroup B and "Other" mtDNAs in Alaskan Eskimos and Aleuts (Merriwether et al. 1994) were acquired through gene flow with non-Eskimo-Aleut populations.

There has also been considerable regional differentiation in haplogroup distribution in Siberia and Asia. Mitochondrial DNA data have been used to suggest that Mongolia and the Lake Baikal region are the source area for ancestral Native Americans, because populations from these regions have polymorphic frequencies of haplogroups A–D (Derenko et al. 1999, 2000; Kolman et al. 1996; Merriwether et al. 1996; Sukernik et al. 1996). However, it is now known that haplogroup A–D mtDNAs are found together in populations originating as far west as the Altai Mountain region to Japan and Korea in the east, with Mongolia and the Lake Baikal region falling in between the two extremes (Ballinger et al. 1992; Derenko et al. 1999, 2000; Horai et al. 1996; Kolman et al. 1996; Merriwether et al. 1996; Schurr et al. 2000; Sukernik et al. 1996; Torroni, Miller et al. 1994). Thus, if the presence of all four founding haplogroups in an Asian population is the sole criterion for identifying the potential source area of ancestral Native Americans, then the range of possibilities has now been expanded beyond Mongolia per se.

Haplogroups A–D actually represent a minority of mtDNA lineages in Siberian and East Asian populations, with various other Eurasian and Asian haplogroups comprising the rest of their mitochondrial gene pool. In fact, most Siberian populations have only haplogroups A, C and D (Derenko et al. 1999, 2000; Schurr et al. 1999; Starikovskaya et al. 1998; Sukernik et al. 1996; Torroni, Sukernik et al. 1993). With few exceptions, Siberian groups lack haplogroup B mtDNAs, and those which do have these haplotypes inhabit the southern margin of Siberia adjacent to Mongolia and northern China (Derenko al. 1999, 2000; Kolman et al. 1996; Petrishchev et al. 1993; Schurr et al. 1999; Shields et al. 1992, 1993; Starikovskaya et al. 1998; Sukernik et al. 1996). In addition, Siberian and East Asian populations appear to lack haplogroup X mtDNAs (Horai et al. 1996; Schurr et al. 1999; Starikovskaya et al. 1998; Sukernik et al. 1996; Torroni, Sukernik et al. 1993), raising questions about the origin of this mtDNA lineage in Siberia and the Americas. Various other Eurasian and Asian haplogroups constitute the rest of the Siberian mitochondrial gene pool. This distribution probably reflects population dynamics in Siberia before and after the colonization of the New World, such as the expansion of Paleoasiatic speakers in northeast Asia (Schurr et al. 1999; Starikovskaya et al. 1998), the spread of Tungusic-speaking populations throughout east and central Siberia (Schurr et al. 1999; Starikovskaya et al. unpublished data; Torroni, Sukernik et al. 1993), the spread of Uralic speakers in northern Asia (Sajantila et al. 1995), and the northward expansion of Turkic speakers into Siberia (Yakuts; Torroni et al. 1998).

Based on these Siberian and Asian mtDNA data, several different models for the peopling of the New World have been developed. Some researchers have suggested that ancestral Amerindian populations brought at least haplogroup A, C, and D mtDNAs from Siberia during the initial colonization(s) of the New World, with haplogroup B possibly representing a second independent migration from East Asia to the Americas (Schurr et al. 1999; Starikovskaya et al. 1998; Torroni, Sukernik et al. 1993). In addition, it was suggested that haplogroup X might also represent a separate migration from somewhere in Eurasia, given its absence in Siberia and much of the Americas (Brown et al. 1998). However, other researchers argue that haplogroups A–D were brought to the New World in a single migratory event (Kolman et al. 1996; Merriwether et al. 1994, 1995, 1996). Indeed, statistical analyses and pairwise mismatch simulations using haplogroup A–D data tend to support a single migration to the New World (Bonatto and Salzano 1997; Stone and Stoneking 1998), although these studies did not account for the RFLP haplotype differences in Amerinds, Na-Dené Indians, and Eskimo/Aleuts.

The antiquity of these haplogroups and the timing of their initial entry into the New World have also been keenly debated. Recent studies have provided ages for haplogroups A–D and X of between 35,000 and 20,000 yr B.P., based on several different statistical estimates (Bonatto and Salzano 1997; Brown et al. 1998; Forster et al. 1996; Schurr et al. 1999; Stone and Stoneking 1998). Similar divergence estimates have been obtained for these lineages in both Asia/Siberia (Horai et al. 1996; Schurr et al. 1999; Starikovskaya et al. 1998; Torroni, Sukernik et al. 1993) and Europe (Torroni et al. 1996, 1998). Additional support for these data comes from the fact that Native American and Siberian populations lack any mtDNAs in common, even those that appear to be identical on the basis of their RFLP haplotypes due to having different CR sequences (Schurr et al. 1999; Starikovskaya et al. 1998; Torroni, Schurr et al. 1993). These findings imply that estimates of haplogroup divergence reflect the genetic diversity that has accumulated in the American branches of these mtDNA lineages, hence, the time at which modern humans first entered the Americas.

However, other investigators have argued that the ca. 25,000 yr B.P. divergence times for these haplogroups of the New World are overestimates of the time at which the colonization process took place, and instead represent the age of the haplogroup divergence in Asia, hence, that of the common ancestral population (Shields et al. 1993; Ward et al. 1991). Using a different coalescent method, Shields et al. (1993) proposed a "late" entry time (12,000–14,000 yr B.P.) of ancestral Amerindians to the New World rather than an "early" entry time, along with the late expansion of northern populations in the circumarctic region (5,000–7,000 yr B.P.). This late entry time for ancestral Amerindians falls within the lower bounds of other divergence time estimates for Native American haplogroups (Bonatto and Salzano 1997; Stone and Stoneking 1998). However, it was based on data taken from Northwest Coast Amerindian and circumarctic populations who are known to share a number of CR sequences from haplogroups A, C and D, and thus could be an underestimate of this date (Lorenz and Smith 1997; Schurr et al. 1999; Shields et al. 1993; Starikovskaya et al. 1998; Ward et al. 1993). On the other hand, the late entry time for circumarctic populations is consistent with other estimates of mtDNA diversity in these same groups (Saillard et al. 2000; Starikovskaya et al. 1998).

In addition, it has been proposed that the ancient haplogroup divergence dates are inflated because they did not consider that multiple variants (i.e., founding haplotypes) from haplogroups A–D were brought to the Americas by ancestral Amerindian populations, namely, haplotypes A1/A2, B1/B2, C1/C2, and D1/D2 (Bailliet et al. 1994; Easton et al. 1996; Merriwether et al. 1994, 1995). However, the hypermutability of the HaeIII 16517 site that is used to delineate these haplotypes (Ballinger et al. 1992; Chen et al. 1995; Torroni et al. 1992; Torroni et al. 1996, 1998; Torroni, Chen, et al. 1994; Torroni, Miller, et al. 1994; Torroni, Neel, et al. 1994; Torroni, Schurr, et al. 1993; Torroni, Sukernik, et al. 1993) raises serious questions about their validity as founding mtDNAs. Therefore, it is reasonable to exclude them from these calculations until stronger evidence for their existence is established.

Y Chromosome

Many new and exciting insights into the peopling of Siberia and the New World have been recently obtained through studies of Y-chromosome lineage distribution in these two regions. The Y chromosome exhibits strict paternal transmission and encompasses large regions of non-recombining sequence, thus offering the possibility for studies of male migration. Although the Y-chromosome sequence evolution rate is slower than that of the mtDNA, it contains several different types of polymorphic systems that have different mutational mechanisms and rates. These include single-nucleotide polymorphisms (SNPs), small insertions or deletions (indels), and short tandem repeat (STR) polymorphisms, also known as microsatellites, with the latter mutating more rapidly than the other two kinds of polymorphisms. All these polymorphisms, or genetic markers, can be used to construct compound haplotypes that are informative for tracing male migration and ascertaining phylogenetic relationships among various populations (Hammer 1995; Jobling and Tyler-Smith 1995).

Because of the variety of polymorphic systems present in the Y chromosome, researchers have adopted a genealogical approach based on a hierarchical analysis of different marker systems to identify paternally inherited haplotypes (Jobling and Tyler-Smith 1995; de Knijff et al. 1997; Lell et al. 1997; Santos et al. 1996). In this approach, sets of Y chromosomes are divided into distinct lineages, or haplogroups, defined by one to several infrequently occurring "biallelic" (present or absent) polymorphisms, such as SNPs or indels. These haplogroups are further assayed for diversity using more variable loci such as STRs, in which multiple alleles of different sizes are present within a population. The resulting "compound haplotypes" comprising biallelic and multiallelic markers are then compared with those occurring in

various world populations to reconstruct the genetic prehistory of these groups. By combining the different marker systems, one can obtain additional information about the demographic history of these haplogroups while minimizing the effect of recurrent mutation in the multiallelic polymorphic systems.

Over the past five years, various research groups have analyzed different sets of biallelic and multiallelic markers to characterize Y-chromosome variation in Siberian and Native American populations. However, only a subset of these biallelic markers have been especially effective for defining the Y haplotypes and paternal lineages present in them, including the DYS287 (M1), DYS199 (M3), M9, DYS7C, RBF5/Tat (M46), M17, and RPS4Y (M130) loci (see descriptions below). In addition, a number of Y-chromosome STRs have been surveyed for variation in these populations, including the DYS19, DYS388, DYS389, DYS390, DYS391, DYS392, and DYS393 loci (de Knijff et al. 1997; Kayser et al. 1997; Lell et al. 1997, 1998, 1999; Santos et al. 1999; Santos, Gerelsaikhan, et al. 1996). These loci represent both tri- and tetranucleotide repeat motifs, as well as different kinds of repeat motifs within an STR class, e.g., $(ATA)_n$ versus $(GTA)_n$ within trinucleotide repeats. For this reason, Y-chromosome variation will be discussed in terms of the haplotypes defined by these informative biallelic and microsatellite markers. Because large numbers of both individuals and populations have been screened for these markers using PCR-based assays, it is possible to make direct comparisons of marker and haplotype frequencies within them.

All studies to date have indicated that at least six major paternal haplogroups are present among Siberian populations. These include the M9, M9/M13, M9/M17, M9/DYS7C/M46, M1 and RPS4Y lineages, although the characterization of additional SNPs will likely reveal further subdivisions within them. As shown below, not all these Y lineages were disseminated into the Americas, and those that were may not have been brought to the New World through a single population expansion. To draw out these distinctions more clearly, each lineage and its distribution in Siberia and the Americas will be separately described.

It should also be stated here that the data sets generated in studies of Y-chromosome variation are usually not entirely equivalent because different arrays of SNPs and STRs have been used in different studies. As a consequence, the nomenclatural system used to define individual Y haplotypes and the paternal lineages to which they belong varies according to a particular study or set of related studies (Hammer et al. 1997, 1998; Karafet et al. 1997, 1999; Lell et al. 1997, 1998, 1999; Santos et al. 1996; Santos et al. 1999). The system used in this paper focuses on the presence or absence of specific biallelic markers in Native American and Siberian Y-chromosomes, and the Y lineages that they define, rather than any particular published nomenclature.

The M9 lineage, which is defined by a C→G transversion at the M9 locus, defines one of the two major branches in human Y-chromosome lineage evolution. It essentially divides all non-African Y-chromosomes from African chromosomes, which, in turn, are defined by either the M1 polymorphism or the ancestral A1 haplotype (Hammer et al. 1997; Underhill et al. 1997). Based on existing data sets, most East Asian and Siberian Y haplotypes exhibit the M9 G allele, hence represent the forms derived from ancestral African haplotypes; and the same general pattern is also seen in Native American populations (Hammer et al. 1997; Karafet et al. 1999; Lell et al. 1998, 1999; Underhill et al. 1997). In the case of Asian, Siberian, and Native American Y haplotypes, the M9 polymorphism is associated with the M3, M46/DYS7C, and M17 SNPs, but not the RPS4Y or M1 markers. Overall, the M9 lineage comprises a minority of the Y haplotypes seen in northeastern Siberians (Hammer et al. 1997; Karafet et al. 1999; Lell et al. 1998, 1999; Underhill et al. 1997).

Defined by an additional C→T transition at the M3 locus, the M9/M3 lineage occurs in a significant proportion of Native American Y chromosomes (Bianchi et al. 1996, 1998; Karafet et al. 1997, 1999; Lell et al. 1997, 1998, 1999; Santos et al. 1999; Underhill et al. 1996), but has yet to be found in any African or European populations (Karafet et al. 1999; Santos et al. 1999; Underhill et al. 1996, 1997). The M9/M3 lineage is present at significant frequencies in most Native American populations, ranging in frequency from 0–56 percent in North America, 57–85 percent in Central America, and 48–100 percent in South America, thereby revealing a general north-to-south cline within the New World (Bianchi et al. 1996, 1998; Karafet et al. 1997, 1999; Lell et al. 1997, 1998, 1999; Santos et al. 1999; Underhill et al. 1996). New STR data also revealed significant differences in both Y lineage and haplotype distributions between North/Central and South American Amerindian populations, suggesting different population histories for the two major continental regions (Bianchi et al. 1998; Karafet et al. 1999; Lell et al. 1998, 1999; Ruiz-Linares et al. 1999; Santos et al. 1999).

In contrast, among Siberian and Asian populations, the M9/M3 lineage has only been observed in the Siberian Eskimos and the Chukchi (Karafet et al. 1997, 1999; Lell et al. 1997, 1998, 1999; Underhill et al. 1996), along with a single Even individual (Karafet et al. 1997, 1999). Given that southeastern Siberia or Mongolia has been proposed as a potential geographic source for ancestral Native American populations (Kolman et al. 1996; Merriwether et al. 1996; Neel et al. 1994; Sukernik et al. 1996), and that the M9 lineage has been suggested to have arisen in this same geographic region (Karafet et al. 1999; Lell et al. 1999; Santos et al. 1999), the absence of the M9/M3 lineage in nearly every Siberian ethnic group and central Asian populations implies that it evolved in the ancestral Native American population(s) after leaving this part of northern Asia, either in Beringia or in the Americas.

The origination of the M9/M3 lineage before the first New World colonization event is also consistent with its presence in all the major linguistic subdivisions of Native Americans. Based on this evidence, it appears that the M3 SNP was maintained in the ancestral Beringian population(s), which subsequently became separated from the populations living further south in the Americas due to glacial barriers (Rogers 1986; Rogers et al. 1991, 1992). This Beringian population(s), in turn, became ancestral to modern-day Eskimo-Aleuts and Chukchi, who are postulated to have had a Beringian origin based on their genetic affiliation

with other circumpolar populations (Forster et al. 1996; Schurr et al. 1999; Shields et al. 1993; Starikovskaya et al. 1998; Szathmary 1984, 1985, 1993). Thus, the presence of the M3 SNP in the Chukchi may be attributable to its presence in the ancestral population of the Paleoasiatic-speaking groups of northeastern Siberia (Lell et al. 1997, 1998, 1999), although others have suggested it resulted from back-migration and gene flow from Alaskan Eskimos westward across the Bering Strait (Karafet et al. 1997, 1999).

Not surprisingly, considerable effort has been made to estimate the age of the M9/M3 lineage, given that it signals the entry of ancestral populations into the New World. An initial study provided an age estimate for this lineage of 30,000 yr B.P., based on the linkage of the M3 C→T mutation and the DYS19 alleles (Underhill et al. 1996) and an autosomal microsatellite mutation rate of 1.5×10^{-4} (Weber and Wong 1993). However, an alternative mutation rate of 2.1×10^{-3} for the DYS19 locus gave an age for the M9/M3 lineage of 2147 yr B.P. (Underhill et al. 1996). Although this lineal age severely underestimated the date for the colonization of the New World, it raised the possibility that the M3 marker arose in an ancestral Beringian or American population after the initial entry of human populations into the New World. Hammer et al. (1998) arrived at a similar conclusion, as their nested cladistic method of Y haplotype analysis provided a M3 mutation age of ca. 10,000 yr B.P. By contrast, Forster et al. (2000) recently estimated a 20,000 yr B.P. age for the M3 mutation based on a mutation rate of 2.6×10^{-4} mutations/20 years for slowly evolving Y STRs. Thus, there are some discrepancies in dating the entry of ancestral Y chromosome lineages into the Americas.

These differences in age estimates probably reflect the different mutational rates of different kinds (tri-, tetra-, penta-) of Y-chromosome STRs (de Knijff et al. 1997; Kayser et al. 1997). The mutation rate of a given STR can also vary considerably depending on the size (number of repeats of the variable block) of the founder allele at each STR locus (Carvalho et al. 1999). On the other hand, Heyer et al. (1997) reported that Y STRs have mutation frequencies comparable to those on the autosomes, roughly equal to that originally published by Weber and Wong (1993). In addition, recent work suggests that STRs have a more rapid mutation rate than previously estimated, meaning that modern human populations spread into different parts of the Old and New Worlds later than estimated in earlier genetic studies (Thomson et al. 2000). Judging from these data sets, more focused studies of STR evolution in Amerindian populations are clearly needed to address the issue of the date(s) of the initial colonization of the New World from a Y-chromosome perspective.

In this context, it should also be mentioned that several other studies of Y-chromosome variation in Siberian and Native American populations used a different set of biallelic and STR loci to characterize Y haplotype variation, including the alphoid heteroduplex (ah) type II gene (Bianchi et al. 1997, 1998; Pena et al. 1995; Santos et al. 1996; Santos et al. 1999). These studies also revealed the presence of a major founding Y haplotype or lineage in Native American populations defined by the ahII/DYS19/M3 markers, one which almost certainly is synonymous with the M9/M3 lineage, and showed that its ancestral form originated somewhere in central-east Siberia. In addition, Bianchi et al. (1998) estimated the age of the ancestral Native American-specific Y lineage of 22,270 yr B.P., a date that was consistent with the age estimates of Underhill et al. (1996) and Forster et al. (2000). Thus, most analyses of Y chromosome variation in Native American populations suggest an "early" rather than a "late" entry of ancestral populations into the New World.

The M46/DYS7C lineage is defined by two different mutations, a T→C transition at the RBF5 locus, and a 50-bp deletion at the DYS7C locus. In fact, the M46 lineage is now known to subsume all the DYS7C haplotypes seen in the same groups (Karafet et al. 1999; Lell et al. 1998, 1999, 2000). Based on the distribution of this lineage, it appears that there has been a substantial paternal genetic contribution of Asians to northern European populations such as the Finns and Saami, as well as an expansion of Uralic-speakers eastward into northern Asia (Jobling et al. 1996; Karafet et al. 1999; Lahermo et al. 1998; Lell et al. 1998, 1999, 2000; Santos et al. 1999; Zerjal et al. 1997). Recent studies also suggest that the derived M46-C allele arose in southeastern Siberia, since this is where the ancestral form of the M46/DYS7C lineage appears (Karafet et al. 1999; Lell et al. 1998, 1999, 2000; Zerjal et al. 1997), with the ancestral populations bearing these haplotypes then influencing the Kets, Altayans and Buryats, as well as Mongolians, Yakuts and Chinese Han populations (Karafet et al. 1999; Lell et al. 1998, 1999, 2000; Santos et al. 1999; Zerjal et al. 1997).

Interestingly, the derived M46/DYS7C haplotypes are common in northeastern Siberian groups, including the Chukchi and Siberian Eskimos, but occur far less frequently in Amur River groups (Karafet et al. 1999; Lell et al. 1998, 1999, 2000). In addition, they are completely absent in Native American populations with the exception of the Navajo, in which a single haplotype bearing the DYS7C mutation has been detected (Karafet et al. 1999; Lell et al. 1998, 1999, 2000; Santos et al. 1999; Zerjal et al. 1997). This distribution suggests that the M46/DYS7C lineage arose in Siberia after the initial settlement of the New World, possibly only 4,000–2,000 years ago (Hammer et al. 1998; Zerjal et al. 1997), perhaps with the expansion of reindeer-herding culture in northern Asia and Eurasia (Zerjal et al. 1997).

The RPS4Y (M130) lineage is defined by a C→T transition occurring at np 711 within the 7th exon of the RPS4Y (ribosomal protein S4 gene on the Y-chromosome) locus (Bergen et al. 1996, 1999). Unlike some of the other Y haplogroups, the M130 lineage appears to be quite ancient and widespread in East and Southeast Asia, appearing in populations as far apart as Australia and Chukotka (Bergen et al. 1996, 1999; Karafet et al. 1999; Lell et al. 1998, 1999, 2000). Based on the STR patterns for its Y haplotypes in Siberian populations, the M130 lineage appears to have arisen in East Asian populations (Bergen et al. 1999; Lell et al. 1998, 1999, 2000), rather than the Altai-Sayan/Lake Baikal region, where nearly all other Y lineages are thought to have evolved. This interpretation is supported by the high frequencies

and diversity of haplotypes in the M130 lineage in the Amur River region and northeastern Siberia (Lell et al. 1998, 1999, 2000). In fact, while sharing founding haplotypes, both Kamchatkan and Amur River populations have distinct sets of RPS4Y haplotypes, implying the considerable divergence of this haplogroup in East Asia.

Based on STR allele distributions, this lineage appears to have spread westward from the Russian Far East into the Baikal region, where it appears at significant frequencies in Central Asian and Central Siberian populations (Bergen et al. 1999; Karafet et al. 1999; Lell et al. 1998, 1999, 2000). However, in the Americas, the M130 lineage has only been seen in the Na-Dené-speaking Tanana and Navajo and Amerindian Cheyenne (Bergen et al. 1996, 1999; Karafet et al. 1999; Lell et al. 1998, 1999). Because the STR allele sizes for the Navajo haplotype are consistent with those present in M130 haplotypes in Siberian groups (Lell et al. 1998, 1999, 2000), it appears that this Y lineage was passed into Na-Dené Indian and Amerindian populations through the secondary expansion of Beringian populations into the New World.

The M1 lineage is defined by an Alu element insertion at Yq11, which has also been called the Y Alu Polymorphic element (YAP) (Hammer 1994). This lineage appears at intermediate to high frequencies (46–78 percent) in African populations and at low frequencies (0–11 percent) in European populations (Hammer 1994; Lahermo et al. 1998; Spurdle et al. 1994). It has also been detected at low to moderate frequencies in Central and East Asian populations, such as the Japanese (Hammer and Horai 1995), Koreans (Kim et al. 1998), Tibetans, Mongolians, Yakuts, Altayans and Tuvinians (Hammer et al. 1997; Karafet et al. 1997, 1999; Lell et al. 1997, 1998, 1999, 2000). However, the Asian M1 haplotypes differ from those in African populations by having longer 3' oligo (dA) tails on the Alu element, and also lack the DYS271 (M2) SNP, an A→G transition that results in an *Nla*III site loss, and which has been found only on African M1 chromosomes (Seielstad et al. 1994).

In the New World, the M1 lineage has been observed in several Native American populations, the Mixe from southern Mexico (Karafet et al. 1999; Lell et al. 1997), the Seminoles of Florida (Huoponen et al. 1997), and several Central and South American populations (Karafet et al. 1999). The two Mixe with the M1 haplotypes also exhibited DYS1 alleles previously observed in other non-Native American populations (Lell et al. 1997), and the Central and South American Indian groups exhibited additional SNPs that typically occur in African M1 haplotypes. Therefore, it appears that these Native American populations acquired their M1 haplotypes through intermarriage with persons having non-native ancestry.

In addition to the above-mentioned SNPs, a number of other SNPs have recently been shown to be phylogenetically informative (Underhill et al. 1997). These mutations mostly define the interior portion of the Y-chromosome phylogeny, i.e., the subbranches of the M9 major lineage. Among those informative for Siberians and Native Americans is the M17 marker, a 1-bp deletion, which defines the M9/M17 lineage. This lineage is present at low frequencies in a small, but not insignificant, number of Siberian populations and occurs at the highest frequency among the Itel'men, whereas it is absent from the neighboring Koryaks (Lell et al. 1998, 1999, 2001). However, the M9/M17 lineage is completely absent from Native American populations, with the exception of the Guaymi (Ngöbé), a Chibcha-speaking tribe from Costa Rica (Lell et al. 1998, 1999, 2000). Because the STR pattern for this Guaymi M9/M17 haplotype is consistent with those present in Siberian groups, it appears to have been brought to the Americas through a secondary expansion of ancient Asian peoples, rather than with the initial immigrants to the New World.

A few Y haplotypes found in Native American populations did not fit into any of the known paternal lineages, hence were placed into an "Other" category. However, it is likely that additional screenings for newly discovered SNPs will further define their origins and affinities, hence the regional source of these haplotypes. In this regard, screening Asian/Siberian and Native American populations for the STR markers observed in Southeast Asian and Chinese populations (Parra et al. 1998; Su et al. 1999) will likely illuminate the origins of Siberian of Native American populations.

From a Y-chromosome perspective, there are clear linkages between Siberia and the Americas, as well as population dynamics within Siberia itself, that have led to the distribution of various paternal lineages within it. These linkages can be summarized as follows. First, at least six different paternal lineages have been identified in Siberia and the Americas using biallelic and STR markers (M9, M9/M3, M9/DYS7C/M46, M9/M17, M130, and M1). Only two of these (M9 and M9/M3) fundamentally contributed to the initial peopling of the New World, either through single (Bianchi et al. 1998; Santos et al. 1999; Underhill et al. 1996) or multiple (Karafet et al. 1999; Lell et al. 1998, 1999, 2000) migration events. Three of the other major Y lineages present in Siberia either arose after the colonization of the New World, being distributed almost exclusively in Siberia (M9/DYS7C/M46, M9/M17), or else originated outside of the geographic region from which ancestral Native American populations bearing the M9 and M9/M3 lineages evolved (M130). One or more later, secondary expansions of human groups from Beringia into the Americas brought with them a different set of M9 haplotypes and the M9/M17 lineage, with the M130 lineage possibly being contributed from the Amur River region. On the other hand, M9/DYS7C/M46 haplotypes appear not to have been introduced into the New World at any appreciable frequency, being dispersed in Siberia and Eurasia during the Neolithic. Finally, the M1 haplotypes present in Native American populations were acquired through non-native admixture, rather than being contributed by founding Asian populations.

Overview of Data

Given all these genetic data, what general patterns of biological affinities and origins for Native Americans can be ascertained? To begin with, all these studies support the Asian origin of Native American populations. Most of them have suggested a region extended from the Altai Mountains to southeastern Siberia and northern China as the potential source area(s) for ancestral

Native American populations. However, the mtDNA data also suggest a possible Eurasian genetic influence with presence of haplogroup X in North America, and Y chromosome data suggest both south-central and eastern Siberia as the source area for ancestral Y lineages brought to the New World. Other data sets suggest possible population contacts with Asian populations from China (Novick et al. 1998) or Polynesia (Cann and Lum 1996; Lum et al. 1994) after the peopling of the New World, but these putative contacts have not been supported by other genetic data (Bonatto et al. 1996). On the other hand, various data sets further reveal post-Columbian (historical) admixture with peoples of European and African descent (e.g., Bortolini et al. 1997; Bravi et al. 1997; Huoponen et al. 1997; Rodriguez-Delfin et al. 1997; Torroni, Chen, et al. 1994), but these data are less important for reconstructing the prehistory of the New World.

While there is a general consensus about the source area for ancestral Paleoamerican populations, there is much less agreement among these studies about the number of migratory events bringing these populations to the New World. The number of possible migrations that have been proposed range from one (Bianchi et al. 1998, 1999; Merriwether et al. 1994, 1995; Monsalve et al. 1998; Novick et al. 1998; Santos et al. 1999), two (Karafet et al. 1999), three (Williams et al. 1985), to four (Horai et al. 1993; Lell et al. 1998, 1999, 2000; Schanfield et al. 1990; 1992; Schurr and Wallace 1999; Torroni, Schurr et al. 1993), depending on the genetic data and the definition of "migration" being used in a particular study. The primary debate taking place in these studies is whether the "Amerind" linguistic/genetic stock represents a single expansion event, or instead the consequence of multiple population movements into the New World. In this respect, should certain molecular data sets be correct in indicating that multiple migrations contributed to the genetic diversity of Amerindian populations, then Amerind cannot represent a single linguistic stock as previously asserted by Greenberg (1987). Regardless of the number of migrations that reached the New World, however, all these data sets are consistent in showing the distinctiveness and the great haplotypic diversity of members of the so-called Amerind linguistic group relative to those from the Eskimo-Aleut and Na-Dené groups, hence the earlier immigration of ancestral Amerindians to the New World.

Perhaps the most controversial aspect of recent molecular studies is the early colonization dates for the Americas that they have suggested. Most archaeological studies have dated this event to between 18,000 and 12,500 yr B.P., whereas genetic studies have provided somewhat older dates ranging from 35,000 to 15,000 yr B.P. (Bianchi et al. 1998; Cavalli-Sforza et al. 1994; Forster et al. 2000; Schurr et al. 1999; Torroni, Schurr et al. 1993; Underhill et al. 1996), again depending on the genetic system being used. The later times have been associated with the entry of the Clovis lithic culture in North America (Greenberg et al. 1986; Merriwether et al. 1994, 1995), while the earlier ones have been used to support the presence of pre-Clovis lithic traditions in North and South America (Schurr and Wallace 1999; Torroni, Neel et al. 1994; Torroni, Schurr et al. 1993; Underhill et al. 1996). Ongoing analyses of the mutation rates of the various genetic systems may ultimately narrow this time range, or perhaps push the initial entry time closer to the dates associated with various archaeological dates in the Americas. Irrespective of the initial entry time, most data sets are concordant in dating the emergence or expansion of the Eskimo-Aleuts and Na-Dené Indians at between 10,000 and 5000 yr B.P., well after ancestral Paleoindians arrived in the New World.

Moreover, all these genetic systems have shown that settlement of the Americas after their initial colonization was not a static process. Although most studies show general genetic divisions between North and Central versus South America, there is also evidence for both north-south and south-north population contact and gene flow between these regions. Underlying these broader patterns is considerable evidence of regional and tribal differentiation of populations in the major continental regions of the New World, particularly South America, with these patterns undoubtedly being shaped by geographic isolation, linguistic differentiation, and genetic drift. In the case of immunogenetic variation, selection appears to have played an especially significant role in producing the variety of protein polymorphism marker, HLA and immunoglobulin haplotypes detected in Siberian and Native American populations. There is also suggestive evidence of selection having acted on specific mtDNA (Torroni et al. 1997) and Y chromosome (Jobling et al. 1998) haplogroups in human populations. Hence, the distribution of maternal and paternal lineages may have been influenced by selection while being disseminated across the globe.

Finally, it should be clear from the discussion of these molecular anthropological studies that analyzing a large number of different genetic markers in human population provides a more complete picture of genetic variation in these groups. We have seen somewhat analogous but not identical views of the peopling of the New World originating from the use of multiple genetic systems. These differences are, in part, due to the varying rates of mutation and mechanisms of sequence evolution that underlie each genetic system, as well as their unique inheritance patterns. Ultimately, some molecular markers may be more informative than others. However, all of them will contribute to the overall understanding of the genetic variation present in Siberian and Native American populations. In this regard, the use of new STR, SNP and RSP data from autosomal loci will further help to delineate these population relationships and genetic diversity.

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