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Autosomal Recessive Diseases Among the Athabaskans of the Southwestern United States: Recent Advances and Implications for the Future

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Genetic and linguistic data suggest that the Na-Dene, of which the Athabaskans are the largest group, are part of a later immigration into the Americas than the first Amerind immigration. Whether a second and third immigration can be separated seems unlikely but continued cross-Bering Strait exchanges may have masked what was a greater separation in the past. The movement of tribes into Siberia appears to have involved a genetic bottleneck leading to at least one disease allele shared by Eskimo/Aleuts and Navajos and a second possibly shared by the Navajo and a Siberian population, but not the same Siberian population that share deep linguistic affinities with the Navajo. A second bottleneck appears to have occurred with the migration of Athabaskans from Northwest North America to the Southwestern United States along the Rocky Mountains. This bottleneck is reflected in several rare recessive diseases shared by the Navajo and Apache. Finally, the Navajo were captured and imprisoned under conditions which led to severe population loss. This, and the "hiding away" of a small number of Navajos in what is now the Western portion of the reservation, led to a Navajo-specific bottleneck(s) resulting in an increased frequency of several rare recessive diseases among the Navajo. Prejudice against human genetic research is high among the Southwestern Athabaskans but attempts to bridge the gap are now occurring. The involvement of Navajo scientists in this process is especially encouraging.

Key words: Athabaskans; Apaches; bottlenecks; Navajos; native Americans

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INTRODUCTION

Many populations pass through "genetic bottlenecks" (periods of reduced population such that future generations are descended from a limited number of people) but relatively few re-expand to create large enough populations to provide multiple cases of diseases caused by the new pool of rare recessive alleles. The Finnish population is one well-known example [De La Chapelle and Wright, 1998]. A less well-known example is the Athabaskans of the Southwestern United States. This is especially true of the Navajo, who now number approximately a quarter million, descended mostly from a population decimated to approximately 5,000 when imprisoned at Bosque Redondo and a smaller number that evaded capture. The Navajo and the Apache share a recent immigration to the Southwestern United States and their movement south as bands along the Rocky Mountains suggests a second, earlier, shared bottleneck. An even earlier bottleneck is suggested for the movement of tribes antecedent to Aleut-Eskimos and Athabaskans into Siberia. In the interval since my previous review [Erickson, 1999], advances in our understanding of Athabaskan (Na-Dene) linguistic and genetic affinities have occurred, new diseases have been described, and many of the disease-causing genes have been identified. The distribution of some of the diseases and our understanding of the potential source of bottlenecks have been modified. These advances have implications for genetic screening and counseling.

ATHABASKAN (NA-DENE) AFFINITIES

There have been many new studies on the linguistic and genetic relationships of the Na-Dene linguistic group of which the Athabaskan speakers are the major sub-group. In the following, I will discuss the linguistic and genetic data including shared rare disease mutants that suggest that the Na-Dene are part of a later migration of Siberians into North America. With the increasing realization

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that boats were an early part of the Neolithic "tool kit," back and forth communication across the Bering Strait (thus sharing the two shores of Beringia) may also have contributed to current linguistic and genetic sharing between Siberian and North American populations [Wilson, 2008].

Studies on Na-Dene linguistic affinities go back for over two centuries [Krauss, 1979], but 20th century analyses (frequently ignoring Russian studies) usually cite Sapir [1929] for separating Na-Dene from other Amerind languages. Greenberg [1960] extensively analyzed many Amerind languages and posited three waves of immigration: the early wave of Amerinds, a later wave of Na-Dene speakers, and the most recent wave of Aluet-Eskimos. These data were summarized and related to dental and genetic evidence supporting the three groupings in a classic paper [Greenberg et al., 1986]. Recent research has incorporated new studies on Siberian languages and also has recognized Russian linguistic analyses. Ruhlen [1998] presented lexical evidence that Na-Dene and Yeniseian languages are related. Vajda [2009] added more lexical evidence, and also identified shared grammatical structures, pointing to an ancient genetic linguistic connection between Yeniseian and Na-Dene, proposing the name "Dene-Yeniseian." Yeniseian gets its name from the Yenisei River (the world's fifth largest river) which flows Northward several thousand kilometers West of the Bering Strait. This entails a deep historical connection between Ket (a Yeniseian language) and Navajo. While the separate immigration of Na-Dene speakers is sometimes rejected [e.g., Goebel et al., 2008], the separate, recent immigration of Aluet-Eskimos has wide support.

Although there is linguistic evidence of a Na-Dene language family as separated from other Amerind linguistic groups, the genetic evidence is less clearcut. Mitochondrial (mt)DNA analyses support a clear distinction of Northern Na-Dene from other Amerinds by the absence of the B haplotype, but Southern Na-Dene (Apache and Navajo) share this haplotype with their neighbors [Torroni et al., 1992, 1993]. Analyses of mtDNA from 700-year-old remains in a Mississippian culture cemetery [Stone and Stoneking, 1998] were used to argue for a single wave of immigration but based much of the inclusion of the Na-Dene on data from the Haida which are frequently excluded from the Na-Dene linguistic grouping. Analyses of Eskimo and Aleut mtDNA suggested a Na-Dene/Eskimo shared ancestry with a recent Siberian origin [Saillard et al., 2000; Zlojutro et al., 2006]. Another study "lumping" Na-Dene mtDNA with those of a single early immigration [Fagundes et al., 2008] seems to have depended heavily on Southern Athabaskans who probably share more of their genome with surrounding populations than do Northwest Na -Dene speakers. Other mtDNA studies suggest affinities of the "first," major immigration with Siberian populations currently living in the Alta-Sayan or mid-lower-Amur regions while the second/third immigration showing affinity to populations currently in Amur-Mongolia-Manchuria [Volodko et al., 2008]. Analyses of mtDNA also suggest more recent to-and-fro exchanges (mentioned above) across the Bering Strait [Tamm et al., 2007].

Y-chromosomal DNA analyses also provide somewhat conflicting results about the timing and separateness of the Na-Dene immigration. An analysis depending on Navajos as the Na-Dene population was compatible with two immigration events, an early one derived from populations now living in Middle-Southern Siberia, and a second from a population now found in the lower Amur/Sea of Okhotsk region which was then shared by Na-Dene and other Amerinds [Lell et al., 2002]. These geographical regions only roughly correspond to those of Volodko et al. [2008] for two waves of immigration based on mitochondrial lineages; the tribes studied hardly overlap. A similar study using Chipewyans as the Athabaskan group (and using more markers) again supported a more recent Siberian origin and separateness of Na-Dene Y-chromosomes [Bortolini et al., 2003]. Another study which mostly used Apache and Navajos as the Na-Dene sample (74%) supported the single immigration theory [Zegura et al., 2004]. However, as already mentioned, the Southwestern Athabaskans are more admixed with other Amerinds by a variety of criteria. A combined analysis using mtDNA and Y-chromosome data also supported a separate, second immigration of Na-Dene and Eskimo-Aluets [Schurr and Sherry, 2004].

A variety of autosomal loci have been studied in Native American populations and provide evidence about the multiple immigration theory. HLA analyses have located Na-Dene groups closely with Siberian tribes but quite separately from Aluets [Moscoso et al., 2006, 2008]. A unique variant of thiosulfate sulfurtransferase (22q11.2-qter) has been found in Alaskan Athabaskans which was not shared by nearby Aleuts and Eskimos [Scott and Wright, 1980]: Cavalli-Sforza et al.'s [1994] analysis of up to 200 blood group and protein polymorphisms combines much of the data. They summarized their vast array of data by principle component analysis. The two-dimensional figure of the two principal components places the Canadian and Northern Na-Dene distant from, but fairly close to, Aleut-Eskimos, while the Southern Na-Dene (Apache and Navajo) were separate from, but closer to other Amerinds, again suggesting admixture (Fig. 1). Another multiple component analysis based on

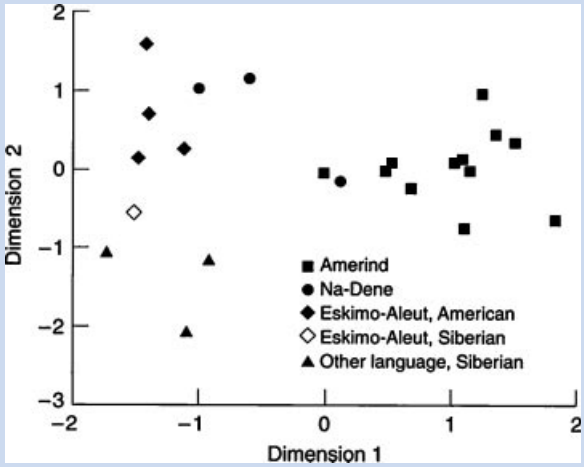

FIG. 1. Two-component analyses by multidimensional scaling of approximately 200 traits in various native American tribes (their population pairwise F_{ST} values calculated from marker frequencies) [Cavalli-Sforza, Luca; THE HISTORY AND GEOGRAPHY OF HUMAN GENES © 1994 Princeton University Press, Reprinted by permission of *Princeton University Press*.

fewer loci did not separate Na-Dene from other Amerinds [Rubicz et al., 2002]. One recent addition to this literature has been phylogenetic analyses of human polyoma virus JC, a commensal virus easily studied in urine samples. The sequences of this benign virus did allow a separation of Na-Dene and other Amerind groups in one study [Fernandez-Cobo et al., 2002] but not in a second study [Zheng et al., 2003].

A rare autosomal recessive disease of increased frequency among both the Siberian Yakuts and Athabaskans is methemoglobinemia due to diaphorase deficiency. Scott [1960] reported a high incidence of diaphorase (DIAE)-deficient methemoglobinemia in Ingalik Indians, a small group of Athabaskans (800 members at the time) living in Alaska. He studied this deficiency in these Athabaskans and in Eskimos that lived close by. Scott [1960] reported a gene frequency of 0.069 for the combined groups. It is not apparent whether much intermarriage occurred in these groups that were located close to each other geographically [Scott et al., 1963]. He subsequently reported multiple cases of this rare disorder among the Navajo [Balsamo et al., 1964]. This disorder also has an increased prevalence among the Yakuts [Nazarenko et al., 2003] and the mutation in *DIAE* was found for this population [Galeeva et al., 2006]. Until such time as the Navajo mutation is described, we will not know if this is a rare mutation shared by decent, but it seems likely.

Another disorder that appears to reflect the more recent immigration of Athabaskans is metachromatic leukodystrophy. This well-known entity due to arylsulfatase A deficiency was found to be increased among the Navajo. Of the three major clinical subtypes, it is the late infantile form, which was multiply diagnosed. The patients were found to be homozygous for IVS4ntl, G → A, abolishing the 5′ splice donor site [Pastor-Soler et al., 1994]. The mutation led to a marked deficiency of mRNA. A careful examination of the birth location of patients and their ancestors disclosed a marked clustering in the western Navajo Nation with no cases observed in the eastern reservation [Holve et al., 2001]. The high incidence in the western Navajo Nation (1/2,520 live births) suggests that this is a result of a genetic bottleneck resulting from a number of individuals who evaded capture by hiding in desolate parts of this region when Kit Carson and the U.S. Army captured most of the Navajos for the "Long Walk" to Bosque Redondo [Williams, 1992]. This same mutation has been found to explain a high incidence of late infantile metachromatic leukodystrophy among the Yupik Eskimos of western Alaska [Pastor-Soler et al., 1995]. As discussed above, the Eskimos/Aleuts may be part of the same second immigration as Na-Dene. It is likely that the Eskimos with increased methemoglobinemia due to *DIAI* deficiency are these same Yupik Eskimos: Scott [1960] only identifies the group with increased *DIAI* deficiency as living on the "Innoko, Yukon, and Kuskokwim Rivers" the latter two rivers bounding the villages where multiple cases of metachromatic leukodystrophy were found [Pastor-Soler et al., 1995].

In summary, genetic and linguistic data suggest that the Na-Dene, of which the Athabaskans are the largest group, are part of a later immigration into the Americas than the first Amerind immigrations. The finding of one rare disease gene allele shared between an Eskimo-Athabaskan population and the Navajo, and the possibility of a second rare disease allele shared between a Siberian native population and the Navajo, supports this relationship. Whether a second and third immigration can be separated seems unlikely, but continued cross-Bering Strait exchanges may have masked what was a greater separation in the past.

APACHE AND NAVAJO AUTOSOMAL RECESSIVE DISEASES

In the following, I will discuss three Mendelian diseases that are found in both the Apache and Navajo tribes. The enrichment of the disease-causing alleles is presumably the result of a genetic bottleneck that took place when relatively small bands moved down along the Rocky Mountains into the southwest [Erickson, 1999, discusses the relevant evidence]. Two of the diseases were first described in the Southwestern Athabaskan population, while the third was not unique for its clinical description.

HOXA1 Deficiency (Formerly Athabaskan Brainstem Dysgenesis)

In the 1990s, clinicians working on the Apache and Navajo reservations encountered children labeled as "Moebius syndrome" because of facial paralyses. However, they were all deaf, showed degrees of central hypoventilation, and had mental retardation. The comparison of a number of these cases led to the realization that they constituted a new entity which was labeled "Athabaskan Brainstem Dysgenesis Syndrome" [Holve et al., 2003].

Clinical features present in all patients include congenital horizontal gaze palsy, hypotonia, sensorineural deafness, central hypoventilation, and developmental delay. Variably present features include swallowing dysfunction, vocal cord paresis, facial paresis, seizures, and cardiac outflow tract anomalies [Holve et al., 2003]. Seven of the patients were Navajo Indians, two children were Apache, and one was of Apache and Pima heritage. One pair of patients was affected sibs. In another family, a sib's death of sudden infant death syndrome (SIDS) suggested that the death was likely caused by the central hypoventilation of Athabaskan brainstem dysgenesis.

Quite independently, a genetic disorder of horizontal gaze palsy (bilateral Duane retraction syndrome, type 3), deafness, and malformations of the cerebral vasculature was being delineated in mostly Saudi Arabian patients. The disorder was called "Bosley–Salih–Alorainy Syndrome" and, finally, fully described in 2007 [Bosley et al., 2007]. Mental retardation and central hypoventilation were not noted among the features common to the syndrome. However, most of the patients had some delay of developmental milestones, and some patients had autistic features. Cardiac defects, which were prominent in the Athabaskan brainstem dysgenesis patients, were not then noted, but absence of the internal carotid artery, sometimes bilateral, was present in some patients. An astute graduate student, Max Tischfield, wondered if the two disorders were related. Consanguinity in the Middle Eastern families aided cloning and the same gene was found to be involved in both disorders, the Navajo and Apache all sharing the same allele [Tischfield et al., 2005] HOXA1 deficiency is the first autosomal

recessive disorder of a *HOX* gene. The mouse knockouts already existed and confirmed the gene's role in brainstem development (particularly rhombomeres 4–7) but did not predict the somatic abnormalities [Chisaka and Cappecchi, 1991; Lufkin et al., 1991]. Thus, internal carotid artery absence and conotruncal heart defects were not found in the mice.

One of the largest differences in the Athabaskans compared to the Middle Eastern patients was the central hypoventilation and mental retardation. A possible explanation for the differences would be hypofunction of genes related to central hypoventilation causing hypoxia and leading to neuronal death. A number of genes have been cloned, mutations in which cause "Ondine's curse" (having to will each breath), scientifically termed congenital central hypoventilation syndrome (CCHS). These include *END1* and *END3* [Bolk et al., 1996], *RET-GDNF* [Amiel et al., 1998], *RNX* [Shirasawa et al., 2000], *BDNF* [Weese-Mayer et al., 2002], *HASH1* [De Pontual et al., 2003], and *PHOX2B* [Amiel et al., 2003]. Of these, *PHOX2B* is the most frequently mutated—in more than 50%, and as high as 97%, of patients with CCHS [Weese-Mayer et al., 2003; Gaultier et al., 2004]. The variation found in *PHOX2B* is almost always a heterozygous expansion of a 20-repeat polyalanine tract in exon 3, increasing to 25–33 repeats. We examined six affected Native American *HOXA1*-deficient patients for the size of their *PHOX2B* exon 3, polyalanine tract following the published protocol [Weese-Mayer et al., 2003]. All were homozygous for the 20 alanine; normal length tract (Erickson, unpublished results). Thus, variation in *PHOX2B* is unlikely to be the cause of central hypoventilation in the Native American *HOXA1*-deficient patients.

As is often the case, once DNA diagnosis was possible, a more extended spectrum of abnormalities was found in *HOXA1*-deficient patients [Bosley et al., 2008]. Congenital heart disease was found in four of the Middle Eastern patients, two of whom had neither deafness nor horizontal gaze restrictions, suggesting the possibility that cardiovascular manifestations might be a clinically isolated manifestation of homozygous *HOXA1* mutations. Importantly, two Navajo patients who were raised at a lower altitude (1,000 m) than most Navajos (~1,500 m) were only mildly cognitively impaired. Thus, cognitive limitations in *HOXA1* deficiency may be secondary to global brain hypoxia precipitated by the combination of central hypoventilation, cerebrovascular malformations, and the relatively high altitude at which most of the Athabaskan population lives. Autism, on the other hand, seems to be a primary, but infrequent sequela of *HOXA1* mutation [Bosley et al., 2007, 2008; Tischfield et al., 2005]. This is of interest given a report of linkage disequilibrium between the autism phenotype and a SNP in *HOXA1* [Ingram et al., 2000].

Poikiloderma With Neutropenia (Formerly Clericuzio-Type Poikiloderma With Neutropenia, Navajo Poikiloderma)

Clericuzio et al. [1991] described "immune deficient poikiloderma" in an abstract in 1991. The disorder starts as a papular erythematous rash on the extremities during the first year of life. It gradually spreads centripetally and, as the papular rash resolves, hypo- and hyperpigmentation results, including telangiectasias (Fig. 2).

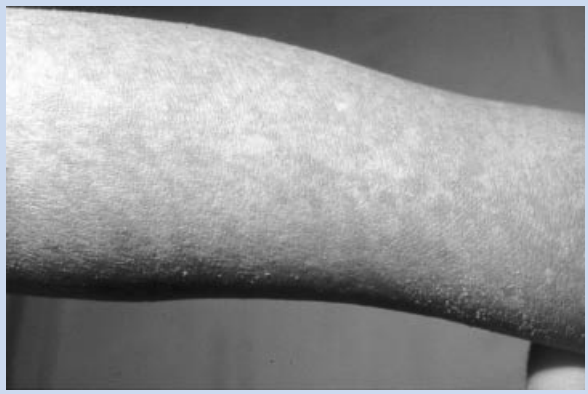

FIG. 2. Forearm of patient with poikiloderma with neutropenia at 3 years of age.

The other skin manifestation is pachyonychia, but alopecia and leukoplakia are distinctively absent. The disorder is not limited to the skin because the patients demonstrate recurrent pneumonias that usually result in reactive airway disease and/or chronic cough. Neutropenia has been variably present and is thought to be cyclical. Decreased neutrophil killing power, but not of the same degree as found in chronic granulomatosis disease, was also reported [Clericuzio et al., 1991].

Originally thought to be limited to the Navajo, there is a clearcut case on the White River Apache reservation, born to Apache parents. The rash first appeared on the child's extremities at 4 months and proceeded centripetally. At 5 years, she is doing well on Keflex prophylaxis. A sibling diagnosed by white blood cell counts at birth died at 2 months of age with pneumonia. The rash is very similar to that of Rothmund–Thompson syndrome which is, however, centrifugal, and cancer has not been found. Nonetheless, some Rothmund–Thomson syndrome patients have been reported with aplastic anemia or myelodysplastic syndrome (might they really have had poikiloderma with neutropenia?) [Rizzari et al., 1996; Knoell et al., 1999; Porter et al., 1999], so mutations in *RECQL4* [also mutated in Baller–Gerold which sometimes has poikiloderma, Rizzari et al., 1996] were sought and not found [Wang et al., 2003]. As expected, typical cases have now been reported in other population groups [van Hove et al., 2000; Mostefai et al., 2008].

Severe Combined Immunodeficiency (SCID)

An excess of apparently typical SCID among the Navajo and Apache was first reported in 1980 [Murphy et al., 1980]. At that time, five cases were described from an estimated population of 150,000, including one pair of siblings. Features were typical of SCID, including early onset of life-threatening infections; low lymphocyte counts with 2–7% T cells; markedly low IgG, IgA, and IgM, and markedly low mixed lymphocyte culture stimulation. At autopsy, one 3-month-old patient showed no lymphocytes in lymph nodes,

thymus, or intestine and the thymus was vestigal and lacked Hassall corpuscles. The rare features of Noma (gangrenous stomatitis, cancrum oris) were found in three Navajo cases [Rotbart et al., 1986]. An attempt to ascertain all cases born to this Navajo population between 1969 and 1982 revealed 11 cases from the study period plus an additional 7 cases [Jones et al., 1991]. Family studies suggested autosomal recessive inheritance with segregation parameters estimates of 0.27–0.38. The gene frequency among the Navajo was estimated to be 2.1%. A higher frequency is likely to be present among the White River Apache.

Morton Cowan's Group did a genome-wide search in 14 Athabaskan-speaking families: 12 Navajo, 1 Apache, and 1 Dine (an Athabaskan-speaking tribe from the Northwest Territories) [Li et al., 1998]. Tight linkage of five markers on 10p was found with the same alleles of the microsatellites found in the Navajo and Apache, while the Dine shared the same allele at the most central marker. At the time of this linkage study, no known SCID genes mapped to the region. Shortly thereafter, deficiency in Artemis, a novel DNA double-strand break repair enzyme involved in V(D)J recombination was identified as a cause of SCID and mapped to 10p [Moshous et al., 2001]. Cowan's group found a unique nonsense mutation in the *Artemis* gene in 21 SCID patients in association with the founder haplotypes they had found on 10p [Li et al., 2002a]. The mutation was found in 17/18 Navajo patients and 3/3 Apache patients. The maternal allele of the Navajo patient with only one copy of the mutation shared a portion of the haplotype and was thought to carry a non-identified regulatory mutation. However, a small deletion, the cause of 60% of *Artemis* gene defects [van Zelm et al., 2008] was not excluded. Of note, despite the suggestion of linkage to *Artemis*, the Northwest territory Dine tribe's mutation was instead found to be in *RAG-1* [Xiao et al., 2009]. The Navajo/Apache SCID mutation may thus have occurred after the initial migration of Na-Dene into North America or been amplified by their shared bottleneck.

With the identification of the gene, prenatal diagnosis and carrier detection were made possible and have since been successfully used [Li et al., 2002b]. Bone marrow transplantation is the major therapy and has been successful with siblings or parents as donors, despite HLA-B mismatches [Murphy et al., 1980]. The finding of much greater success with early transplantation [O'Marcaigh et al., 2001] has motivated newborn screening. The Navajo IRB has recently approved this screening and has introduced its practice at the Tuba City and Chinle Indian Health Service Hospitals (Jennifer Puck, personal communication). The method used, detecting T-cell reception excision circles [Puck, 2007], will detect multiple causes of SCIDs, including X-linked, one case of which has been found among the Navajo [O'Marcaig et al., 1997].

NAVAJO-SPECIFIC DISEASES

As discussed above, the Navajo underwent an additional, severe bottleneck (possibly two parallel events), in the late 1860s. This (or these) event(s) has led to an enrichment of recessive alleles for several diseases, two first described in the Navajo and several more previously well described.

Navajo Neurohepatopathy (Better Called *MPV17* Deficiency, Previously Known as Navajo Neuropathy or Navajo Familial Neurogenic Neuropathy)

Appenzeller and colleagues originally described four Navajo children with anesthesia (leading to corneal ulceration, painless fractures, and acral mutilation), severe weakness, absent or markedly decreased deep tendon reflexes, and normal IQ. Because of its occurrence in an unlike sex sib pair and its uniqueness, they considered it to be an autosomal recessive disorder [Appenzeller et al., 1976]. Their investigations included a sural nerve biopsy on one patient, who was practically devoid of myelinated fibers. They also found high levels of protein in cerebrospinal fluid [Appenzeller et al., 1976]. The initial report by these authors was followed by a description of 11 new patients with the same syndrome and further details on the original four patients [Snyder et al., 1988]. The additional features included systemic infections, macronodular cirrhosis, poor weight gain, and sexual infantilism [Snyder et al., 1988]. MRI imaging of the brain also disclosed white matter abnormalities, suggesting CNS demyelination despite the apparently normal IQ [Snyder et al., 1988].

Children are usually diagnosed at the end of the first year of life or the beginning of the second year of life, either because of the neurological symptoms or liver disease. The liver disease can present as hepatomegaly, persistent neonatal jaundice, or even a Reye-like syndrome of acute hepatic failure in infancy [Holve et al., 1999]. This infantile presentation represents approximately 25% of *MPV17* cases [Holve et al., 1999]. Liver disease or neurological disease may first present in older children. Liver disease has been a frequent cause of death and it has been treated in multiple cases with a liver transplant [Holve et al., 1999]. Siblings may differ by presenting as acute liver failure or the more chronic neurodegenerative form. Weakness and/or corneal ulcerations are the other frequent presenting signs. Confirmation of the diagnosis comes from nerve conduction studies, hepatic function studies, spinal fluid protein determinations; MRI imaging can reveal leukoencephalopathy, primarily of the cerebellum [Snyder et al., 1988], which suggests demyelination. In one survey, the mean age of death was approximately 10 years, frequently due to liver disease [Holve et al., 1999]. With liver transplantation, longer survivals are occurring and at least one patient has developed otherwise unexplained renal failure (Erickson, personal observation). This progression mirrors the underlying metabolic needs of these organs: brain > liver > kidney > other tissues.

The evidence that this is an autosomal recessive disorder remains strong although a formal segregation analysis has not been performed. The 24 cases identified by Singleton et al. [1990] came from 13 families and common ancestors could be identified. The frequency noted in this epidemiological investigation was approximately 1 in 2,500 births for the Western Navajo Reservation, contrasted with 1 in 14,000 births for the Eastern Reservation [Vu et al., 2001]. As with metachromatic leukodystrophy, these authors suggested that this resulted from a bottleneck due to the remnants of the group who hid from the U.S. Army with

possible skewing of distributions after the "Long Walk" [Williams, 1992].

The finding of a decrease in the number of mitochondria in the liver of two patients provided an important clue as to the gene involved [Vu et al., 2001]. Mapping using 400 microsatellite markers in a small number of families showed only one marker that was homozygous in three affecteds and not in some unaffected [Kardimas et al., 2006]. This marker was 1 of 10 that gave pair-wise LOD scores of 1.0 or more and was located near a mitochondrial maintenance gene, *MPV17*. A single homozygous mutation, R50Q, was found in six patients [Kardimas et al., 2006]. This gene had recently been implicated in an infantile hepatocerebral form of mitochondrial depletion syndrome [Spinazzola et al., 2006]. Interestingly, mice deficient in *Mpv17* show the greatest deficiency of mitochondrial DNA in liver, followed by muscle, and with kidney and brain only 50% deficient [Spinazzola et al., 2006]. Such data do not exist for humans, and one wonders if the relative deficiencies will be the same. Of note, the same mutation in *MPV17* has been found in an Italian family but on a very different haplotype [Spinazzola et al., 2008].

Oral–Facial–Digital Syndrome IX With Severe Microcephaly (Navajo-Variant Oral–Facial–Digital Syndrome IX)

We have recently described an oral–facial–digital syndrome among the Navajo which has overlap with oral–facial–digital syndrome IX but differs from it in the very severe mental retardation and microcephaly [Erickson and Bodensteiner, 2007]. Two pairs of siblings, one of mixed sex, shared the constellation of features. An older sib to one of the pairs had died at 6 months of the "same condition." Constant features in these patients are bifid tongue, microcephaly, and short stature. Digital features are less common. Three of the four patients have retinal colobomata. Other oral anomalies have included hamartomas (3/4; Fig. 3), cleft alveolar ridge (3/4), bifid tongue (4/4), and abnormal frenula (2/4). The digital abnormalities have been less complete or less noted: polydactyly in one case and tarsal/carpal shortening in two cases. The microcephaly has been accompanied by brain atrophy and migrational abnormalities.

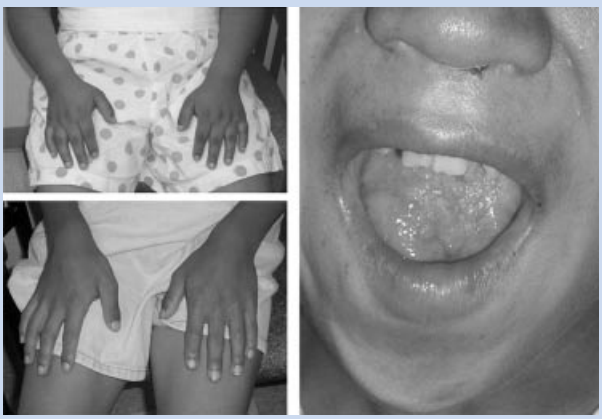

FIG. 3. Patients with Navajo-variant oral–facial–digital syndrome IX. Upper left, mild brachydactyly in patient A; lower left, normal digit length in patient B; right, hamartomas and bifid tongue in patient B.

This constellation of signs shows overlap with oral–facial–digital syndrome IX (OFD IX). This was originally described in two boys, one with lobulated tongue [Gurrieri et al., 1992]. These patients were only mildly mentally retarded and showed slightly notched upper lips. They also showed retinochoroidal colobomas. The marked microcephaly and severe mental retardation are unique Navajo features. The genetic cause remains to be determined.

Microvillous Inclusion Disease

A previously well-described disease of increased frequency among the Navajo (as well as diaphorase-deficient methemoglobinemia and metachromatic leukodystrophy described above) is microvillous inclusion disease [Pohl et al., 1999]. This disorder of intractable diarrhea is nearly always fatal in early life. The patient's biopsies show complete villous atrophy, crypt hypoplasia, and absence of the brush border [Davidson et al., 1978; Phillips et al., 1985]. There was an increase of inclusions within the enterocytes which electron microscopy has shown to be membrane-bound inclusions containing microvilli [Phillips and Schmitz, 1992; Groisman et al., 1993]. Studies of specific transporters have indicated that apical, but not basolateral, membrane transport systems are defective [Michail et al., 1998]. The finding that Rab8 (a small GTP-binding protein involved in localizing apical proteins in intestinal epithelial cells) deficiency in mice causes a pathological picture nearly identical to MID, but only at weaning, further implicated intracellular transport pathways [Sato et al., 2007]. Interestingly, although this group found absent *RAB8* mRNA and protein in one MID patient's biopsy specimen, they did not find mutations in *RAB8* in this or two other patients [Sato et al., 2007].

Recently, mutations in myosin Vb (*MYO5B*) were found in 9 out of 10 separate families with MID-affected members [Müller et al., 2008]. Most of the patients were homozygous for one of eight different mutations, but of note, only heterozygous mutations were found in two early onset patients while a homozygous mutation was found in one late onset case that is managed with more than 50% enteral nutrition, that is, a mild case [Müller et al., 2008]. We identified a shared homozygous mutation (c1977 C → T [P660L]) in *MYO5B* in seven affected Navajos with the expected heterozygosity in five parents [Erickson et al., 2008]. The development of a simple, restriction enzyme-based assay allows for rapid screening of this mutation [Erickson et al., 2008].

Oculocutaneous Albinism Type 2 (OCA2)

The Navajo have an increased frequency of OCA2 which is genetically distinct from that of the nearby Hopi (well known for a high incidence of albinism) [Yi et al. 2003]. The mutation is caused by a LINE-mediated, 122.5 kb deletion of the *P* gene. The haplotype background suggested that this mutation was recent, originating 400–1,000 years ago [Yi et al., 2003]. A three-primer PCR test was developed for carrier detection and the frequency found was

approximately 4.5%. The estimated prevalence of this form of OCA2 was between 1/1,500 and 1/2,000 [Yi et al., 2003].

Xeroderma Pigmentosum (XP)

Xeroderma pigmentosum (XP) is currently known to afflict three pairs of siblings in families from the Eastern Navajo Reservation. There are reports from these parents that there were 10 or 12 similarly affected children in the last few decades. The diagnosis has been confirmed by tests on a skin biopsy (presumably, UV sensitivity). The variant is Cockayne-like with microcephaly and dwarfism. The complementation group and gene involved have not yet been determined.

THE FUTURE

At this point in time, the Navajo IRB has a moratorium on genetic studies. Although the IRB has approved the screening test for SCIDs, and the test involves examining DNA circular molecules, this was not considered a genetic, but rather a disease test. Educational dialogues concerning modern genetic testing may be beneficial to increase awareness among members of the Navajo Nation. In this regard, Dr. Murray Brilliant of the University of Arizona and Dr. Edward Garrison of Diné College organized a meeting entitled "Community Conversations on Genetics" in Shiprock, New Mexico, April, 2009, which was widely advertized to the public. The meeting was sponsored by a wide number of organizations, including the University of Arizona, the University of New Mexico, the National Newborn Screening and Genetics Research Center, The Mountain States Genetics Regional Collaborative Center, The National Coordinating Center for Genetics in Newborn Screening Regional Collaborative Groups, and The Higher Education Institution of the Navajo, Diné College. There was a broad range of participants, including traditional healers and several Navajos with PhDs in biomedical science. Perhaps the most important development from this meeting was that the head of the Navajo IRB heard parents of children with Athabaskan Mendelian diseases speak "loudly and clearly" for their desire for genetic testing. Obviously, there is a need for more such meetings. One issue raised that caused an up-swelling of anger was non-Native American Indians performing genetic research about ethnographic history when consents were obtained only for disease-oriented research purposes. This is perhaps best exemplified by the recent lawsuit of the Havasupai tribe against researchers at the Arizona State University concerning the use of their samples [Rubin, 2004]. However, it became clear that many false notions regarding possible genetic research were present among some of the Navajo participants at the recent "Community Conversation on Genetics" meeting in Shiprock. In the open discussions, several individuals mentioned concerns about exploiting Navajo genes for medical purposes or experimenting with gene therapy on the Navajos. Thus, a considerable amount of education will be needed before sufficient trust develops to allow genetic studies on Athabaskan Mendelian diseases on the Navajo reservation to be performed. Such a dialogue also needs to occur with other Athabaskans, especially the Apaches, and non-Athabaskan Native American tribes. The development of concepts of community-based participatory research by and for Native Americans should provide the basis for new, and appropriate approaches to genetic research [Santos, 2008].

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