

Report

Localization of a Recessive Gene for North American Indian Childhood Cirrhosis to Chromosome Region 16q22—and Identification of a Shared Haplotype

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North American Indian childhood cirrhosis (NAIC, or CIRH1A) is an isolated nonsyndromic form of familial cholestasis reported in Ojibway-Cree children and young adults in northwestern Quebec. The pattern of transmission is consistent with an autosomal recessive mode of inheritance. To map the NAIC locus, we performed a genomewide scan on three DNA pools of samples from 13 patients, 16 unaffected siblings, and 22 parents from five families. Analysis of 333 highly polymorphic markers revealed 3 markers with apparent excess allele sharing among affected individuals. Additional mapping identified a chromosome 16q segment shared by all affected individuals. When the program FASTLINK/LINKAGE was used and a completely penetrant autosomal recessive mode of inheritance was assumed, a maximum LOD score of 4.44 was observed for a recombination fraction of 0, with marker *D16S3067*. A five-marker haplotype (*D16S3067*, *D16S752*, *D16S2624*, *D16S3025*, and *D16S3106*) spanning 4.9 cM was shared by all patients. These results provide significant evidence of linkage for a candidate gene on chromosome 16q22.

North American Indian childhood cirrhosis (NAIC; also known as “CIRH1A” [MIM 604901]) is an isolated nonsyndromic form of cholestasis found in Ojibway-Cree children from First Nations communities in the Abitibi region of northwestern Quebec, Canada (Weber et al. 1981). The disease typically presents, in a child who is otherwise well, with transient neonatal jaundice that progresses to biliary cirrhosis requiring hepatic transplantation in childhood or young adulthood. The

biochemical and histopathologic features of the disease suggest involvement of the bile ducts, rather than of the bile canaliculi. They include elevated gamma glutamyl transferase and alkaline phosphatase levels and, typically, marked fibrosis around portal bile ducts. Results of imaging studies are not typical of known cholangiopathies, such as sclerosing cholangitis. Clinical and physiological investigations to discover the underlying cause of NAIC have been unsuccessful. Under the assumption of autosomal recessive transmission and complete penetrance, the carrier frequency in at-risk populations was estimated to be ~9% (E. Drouin, unpublished data). Hypothesizing that a major founder mutation underlies most or all cases of NAIC, we used a DNA-pooling strategy to search for an excess of shared homozygosity due to identity by descent (Sheffield et al. 1998) among patients, compared with their unaffected first-degree relatives.

Samples were obtained with ethics approval from the Institutional Review Boards of Hôpital Sainte-Justine

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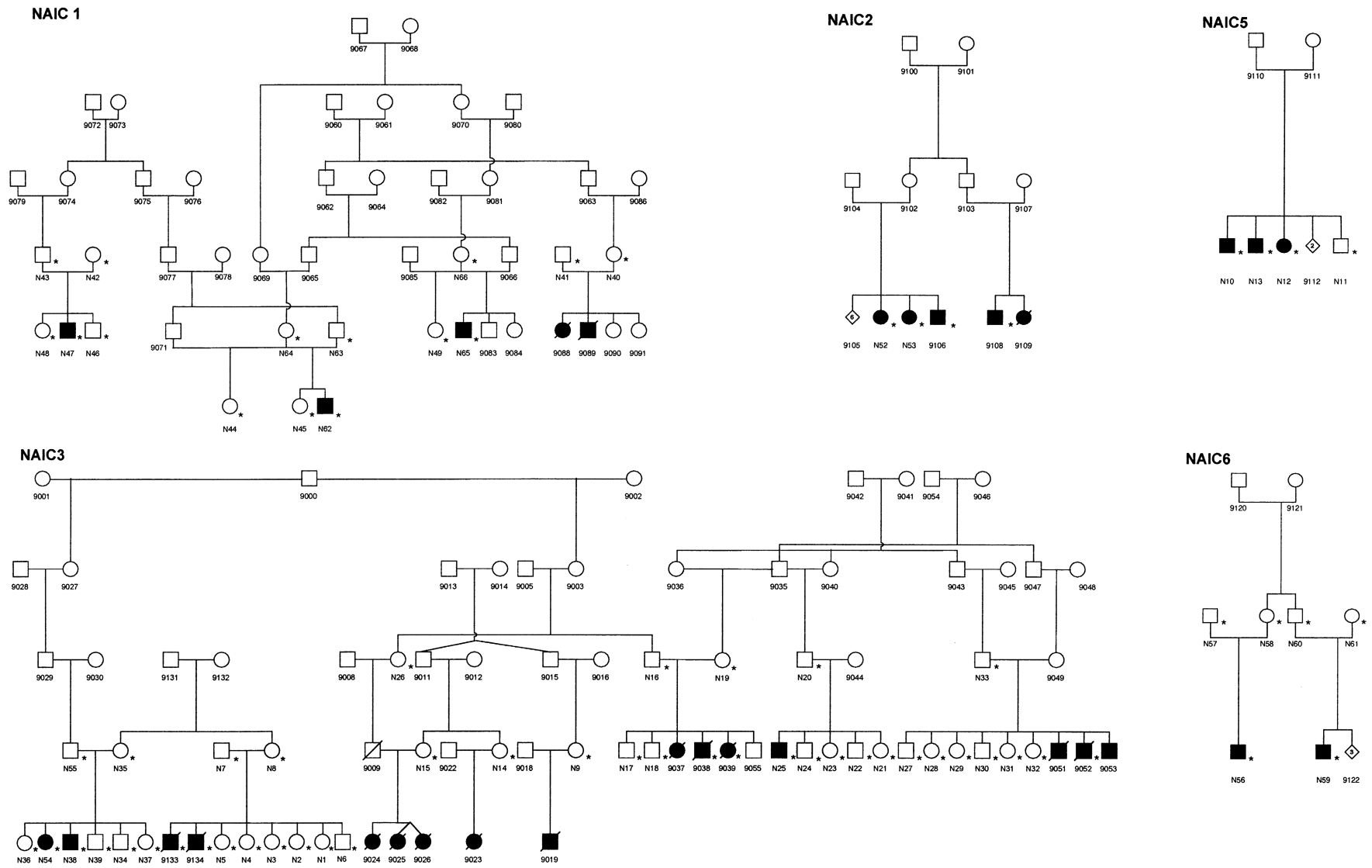


Figure 1 Pedigrees of five families with NAIC. Blackened symbols represent individuals with clinically and biochemically documented NAIC. An asterisk (*) indicates an individual whose DNA sample was genotyped. The identification prefix “N” denotes the initial 51 family members who provided DNA samples for the study; DNA samples from 7 additional NAIC patients (designated “9038,” “9039,” “9052,” “9106,” “9108,” “9133,” and “9134”) became available later and were included in the linkage and haplotype analyses. The number in a diamond-shaped symbol is the number of additional family members for whom DNA samples were not available.

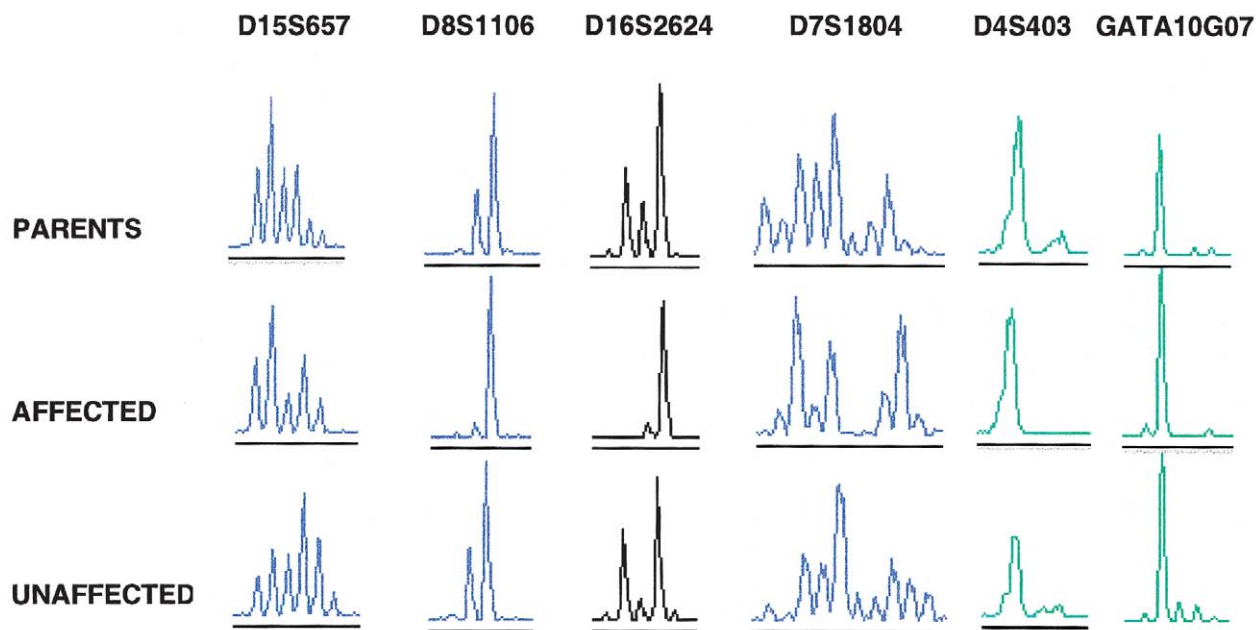


Figure 2 ABI 377 electropherograms for six SSLPs, for three DNA pools (parents, unaffected siblings, and patients). *D15S657* and *D7S1804* are representative markers that have multiple peaks in all DNA pools, corresponding to distinguishable alleles. *GATA10G07* appears to be monomorphic in all three DNA pools. Three markers (*D16S2624*, *D8S1106*, and *D4S403*) had a predominant peak in the DNA pool of affected children but differed by the presence of two or more peaks in the parent and unaffected-sibling pools.

and Montreal General Hospital. Of note, all known patients have been followed by A.R.-W. and/or E.D. Consenting individuals were visited by A.R.-W., E.D., and/or G.A.M., who explained the study and obtained written consent, pedigree information, and blood samples. The detailed clinical features of the patients in the study will be described separately (E. Drouin, unpublished data). Leukocyte DNA samples were obtained from 13 affected individuals, as well as from their parents and unaffected siblings, when available. These 51 individuals from five families are shown, with the identification prefix "N," in figure 1. Three DNA pools were used in the genomewide scan. The three DNA pools contained equal quantities of DNA from the following individuals: all available obligate heterozygote parents ($N = 22$), all 13 affected individuals with identification prefix "N," and unaffected siblings (48, 46, 44, 45, 49, 39, 34, 5, 4, 17, 18, 24, 23, 27, 28, and 11). We limited the number of subjects in the pool of unaffected siblings to two individuals from each nuclear family, to avoid overrepresentation of specific alleles. A genomewide scan was performed with a set of 380 simple-sequence-length polymorphisms (SSLPs). This marker panel is a modified version of the Cooperative Human Linkage Center Human Screening set version 6.0 (Dubovsky et al. 1995) and includes selected Généthon markers (Dib et al. 1996). The three DNA pools were used as templates for DNA amplification. The DNA pool from af-

ected individuals was genotyped in duplicate. Each marker was independently amplified using fluorescently labeled primers (Life Technologies). The PCR products were multiplexed and electrophoretically separated on an ABI 377 DNA sequencer (PE Biosystems) using 5% acrylamide gels. The gels were analyzed with GeneScan version 2.0.2 peak-calling software (PE Biosystems) and were inspected visually to identify markers with a predominant allele in the pools of affected individuals, compared with the DNA pools of the parents and of unaffected siblings. Genealogical data from an additional 79 individuals were used to construct the pedigrees (fig. 1). All patients were of northern-Ojibway or Cree origin and had both a history of neonatal jaundice and clinical and biochemical evidence of a cholangiopathic process. In all patients from whom liver samples were available, the presence of biliary cirrhosis was confirmed. After the initial mapping with pooled DNA, samples from small archived liver samples from an additional seven patients (designated "9038," "9039," "9052," "9106," "9108," "9133," and "9134") became available and were used for further analysis.

After the genomewide scan, selected markers chosen from the Center for Medical Genetics, Marshfield Medical Research Foundation genetic map for chromosomes 4, 8, and 16 were genotyped using individual DNA from the five NAIC pedigrees. Fluorescently labeled oligonucleotides (Research Genetics) were used

Table 1

LOD Scores for Linkage of NAIC and Chromosome 16 Markers

MARKER	GENETIC-MAP POSITION ^a (cM)	LOD SCORE AT $\theta =$						
		.00	.01	.05	.10	.20	.30	.40
<i>D16S3140</i>	74.44	−∞	−1.74	.40	.99	.96	.54	.15
<i>D16S3089</i>	80.00	−∞	−.69	.67	1.05	.94	.54	.17
<i>GATA138C05</i>	81.15	1.41	1.48	1.52	1.37	.91	.46	.13
<i>D16S514</i>	81.15	−∞	.03	1.01	1.25	1.05	.63	.20
<i>D16S3398</i>	84.75	−∞	3.49	3.64	3.28	2.32	1.32	.44
<i>D16S3067</i>	85.94	4.44	4.34	3.85	3.24	1.97	.90	.13
<i>D16S752</i>	87.06	.81	.82	.81	.71	.46	.23	.06
<i>D16S2624</i>	87.62	4.04	3.91	3.40	2.80	1.72	.84	.24
<i>D16S3025</i>	88.18	2.58	2.52	2.31	2.03	1.47	.88	.31
<i>D16S3106</i>	88.18	.44	.45	.43	.37	.23	.11	.03
<i>D16S512</i>	89.63	1.20	1.41	1.76	1.77	1.34	.77	.25
<i>D16S3083</i>	92.10	−∞	−2.17	−.22	.43	.43	.22	.00
<i>D16S3125</i>	93.78	−∞	.91	1.98	2.06	1.54	.85	.24
<i>D16S518</i>	95.08	−∞	−1.80	−.59	−.14	.10	.09	.03

^a Map positions from the Center for Medical Genetics, Marshfield Medical Research Foundation Web site.

for *GATA138C05*, *D16S3398*, *D16S3067*, *D16S752*, *D16S2624*, *D16S3025*, and *D16S518*. ABI 377 gel files were analyzed using an automated allele-calling software package developed by Mark Daly at the Whitehead Institute/Massachusetts Institute of Technology Center for Genome Research. For *D16S3140*, *D16S3089*, *D16S514*, *D16S3106*, *D16S512*, *D16S3083*, and *D16S3125*, the marker alleles were amplified by PCR with one of the primers end-labeled with [³²P]- γ ATP, under standard conditions, and were analyzed as described elsewhere (Richter et al. 1999).

Linkage between the NAIC locus and microsatellite markers was analyzed using the FASTLINK software package (version 4.1P [Cottingham et al. 1993; Schäffer et al. 1994; Schäffer 1996; Becker et al. 1998]) of the LINKAGE programs (version 5.2 [Lathrop and Lalouel 1984; Lathrop et al. 1984, 1986]). ILINK was used for two-point linkage analysis assuming an autosomal recessive trait with complete penetrance. The disease-allele frequency was estimated to be .045. LOD scores were computed from the likelihoods maximized over marker-allele frequencies for selected values of recombination fraction (θ) < .5 and at $\theta = .5$. (Terwilliger and Ott 1994; Annunen et al. 1999). Genetic distances between microsatellite markers were obtained from the Center for Medical Genetics, Marshfield Medical Research Foundation Web site.

The DNA-pooling scheme allowed the genomewide scan to be performed with ~1,500 PCR reactions (4 × 380 markers) loaded onto 14 ABI 377 gels. We scored the ABI 377 trace data for 333 SSLPs, after discarding 47 because of weak, absent, or incorrectly sized PCR products. Three markers (*D4S403*, *D8S1106*, and *D16S2624*) were potential candidates for close linkage

to the NAIC locus, since the affected DNA pools appeared to contain a predominant allele, compared with the control DNA pools (fig. 2).

Available family members were genotyped for *D4S403*, *D8S1106*, and *D16S2624*. All affected individuals were homozygous for the same *D16S2624* allele (143 bp), whereas the marker was polymorphic in the remaining family members. A LOD score of 4.04 at $\theta = 0$ was obtained for linkage of the NAIC locus and *D16S2624*. A single *D4S403* allele was present in 23 of 26 chromosomes from the patients. However, recombination under the assumed genetic model was observed between the NAIC locus and between NAIC and *D4S403* and *D8S1106*. There was little or no evidence for linkage to *D4S403* (and two distal markers) or to *D8S1106*.

Thirteen additional chromosome 16 markers closely linked to *D16S2624* were genotyped. The maximum LOD score was 4.44 at *D16S3067* (table 1). The closest recombinant flanking markers of the NAIC-associated haplotype were *D16S3398* and *D16S3083*, and these define a 7.4-cM interval. Furthermore, all patients were homozygous for a five-marker haplotype, composed of *D16S3067*, *D16S752*, *D16S2624*, *D16S3025*, and *D16S3106* (table 2). The NAIC-associated haplotype is flanked on the centromeric side by *D16S3398* and on the telomeric side by *D16S512*, an interval of 4.9 cM. Two or more alleles of *D16S3398* and *D16S512* were observed in the sample of NAIC chromosomes, suggesting that ancestral recombination events occurred between these markers and the disease locus.

NAIC belongs to a heterogeneous group of autosomal recessively inherited liver disorders characterized by an early onset of cholestasis and progressing to cirrhosis

Table 2

Genotypes for Chromosome 16 Markers Observed in Patients with NAIC

PEDIGREE AND ID	GENOTYPE FOR MARKER ^a													
	<i>D16S3140</i> (74.44)	<i>D16S3089</i> (80.00)	<i>GATA138C05</i> (81.15)	<i>D16S514</i> (81.15)	<i>D16S3398</i> (84.75)	<i>D16S3067</i> (85.94) ^b	<i>D16S752</i> (87.06) ^b	<i>D16S2624</i> (87.62) ^b	<i>D16S3025</i> (88.18) ^b	<i>D16S3106</i> (88.18) ^b	<i>D16S512</i> (89.63)	<i>D16S3083</i> (92.10)	<i>D16S3125</i> (93.78)	<i>D16S518</i> (95.08)
1:														
N47	163/151	184/196	160	121/125	201	142	105	143	104	196	201/205	207	181	279/275
N62	167/151	184/196	160/143	121	201	142	105	143	104	196	201/207	200/212	203/207	283
N65	167/147	182/196	160/152	125	201	142	105	143	104	196	205	209/213	181/207	281/279
2:														
N52	169/165	196	160	125	201	142	105	143	104	196	205	209	203	279
N53	169/165	196	160	125	201	142	105	143	104	196	205	209	203	279
9106	169/165	196	160	125	201	142	105	143	104	196	205	209	203	279
9108	165	196	160	125	201	142	105	143	104	196	205	209	203	279
3:														
N25	165/151	190/194	160/155	121/125	201	142	105	143	104	196	201/207	207/213	203	283/273
N38	167/151	184/192	152	121	213/201	142	105	143	104	196	205/207	209/213	203/205	283/273
N54	165/151	184/192	152	121	213/201	142	105	143	104	196	205/207	209/213	203/205	283/273
9038	165/151	192/196	nd	121/125	201	142	105	143	104	196	201/207	199/207	203/205	273
9039	165/151	192/196	164/152	121/125	201	142	105	143	104	196	201/207	207/213	203	273/283
9052	142	105	143	104	196
9133	142	105	143	104	nd
9134	167/165	186/196	160/152	121/125	213/201	142	105	143	104	196	201/205	207/209	203/205	273
5:														
N10	151	192/194	152	121/125	201	142	105	143	104	196	201	213	183/195	281
N12	151	192/194	152	121/125	201	142	105	143	104	196	201	213	183/195	281/273
N13	169/151	184/194	152	125	201	142	105	143	104	196	201	213	183/195	281
6:														
N56	169/167	184/196	143	125	201	142	105	143	104	196	207	213	203	283
N59	167/147	184/196	143	125	201	142	105	143	104	196	205/207	213	199/203	281/273

NOTE.—Each entry represents the two disease-associated haplotypes of the patient. Where the patient was homozygous for a marker locus, only the allele is given; otherwise the heterozygous genotype is given.

^a An ellipsis (...) denotes that the marker was not typed; nd = Genotype was not determined because it could not be reliably identified.

^b Marker with identical alleles among all patients in the study.

and often to liver failure before adulthood (Gray and Saunders 1966; Toussaint and Gros 1966; Williams et al. 1972). The clustering and segregation pattern of the disease are consistent with a common ancestral mutation causing the disease in all affected individuals. A founder effect is consistent with the demographic history of Canadian Ojibway-Cree (McMillan 1995). Founder effect has been observed, in other Native American populations, for autosomal recessive traits including type I glutaric acidemia (Haworth et al. 1991; Greenberg et al. 1995), pyruvate carboxylase deficiency (Robinson et al. 1984), and limb-girdle muscular dystrophy (Weiler et al. 1996) in Manitoba; for microcephaly-micromelia (Ives and Houston 1980), hyperammonemia-hyperornithinemia-homocitrullinuria syndrome (Camacho et al. 1999), and Sandhoff disease (Lowden et al. 1978) in Saskatchewan; and, possibly, for an infantile leukoencephalopathy in northern Manitoba and Quebec (Black et al. 1988). In addition, founder effect has been suggested for dominantly inherited conditions (Birt and Davis 1975) and multigenic traits, such as type II diabetes and hyperlipidemia (Hegele et al. 1998, 1999).

The multipoint LOD score of 4.44 provides strong support for the location of the NAIC locus on distal chromosome 16q. The observation of a haplotype shared among all five families with NAIC is consistent with the hypothesis that these individuals share the same mutation, which is identical by descent. The 4.9-cM interval defined by *D16S3398* and *D16S512* encompasses the haplotype common to all NAIC-bearing chromosomes and is likely to contain the disease locus.

Clinically, NAIC has been suspected to be distinct from previously described nonsyndromic familial cholestases, because of its marked cholangiopathic features and severe degree of fibrosis on liver histology. Three such disorders, designated "progressive familial intrahepatic cholestases" (PFICs), are caused by mutations in genes coding for canalicular transport proteins. In PFIC-1, mutations in a P-type ATPase gene on chromosome 18q21-q22 cause both Byler disease (Clayton et al. 1969) and benign recurrent intrahepatic cholestasis (Bull et al. 1998). PFIC-2 results from mutations in the sister of the P-glycoprotein gene on chromosome 2q24, which encodes a liver-specific ATP-binding cassette transporter thought to be the human bile salt-export pump (Strautnieks et al. 1998). PFIC-3 is caused by mutations in the multidrug resistance-3 P glycoprotein gene on chromosome 7q21 (de Vree et al. 1998). The present study shows that NAIC is genetically distinct from the three known PFICs. However, other familial infantile cholestases have been reported in Greenland Inuit (Nielsen et al. 1986), Turks (Koçak et al. 1997), and Arab Israelis (Naveh et al. 1997). Available descriptions have not permitted detailed clinical and pathological comparisons with NAIC. It is now possible to test these

patients for linkage to the NAIC locus. The mapping of this locus is an important step toward understanding this frequent and potentially fatal disease of First Nations children in northwestern Quebec.

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Electronic-Database Information

The accession number and URLs for data in this article are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, <http://www.marshmed.org/genetics/>
Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for CIRH1A [MIM 604901])

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