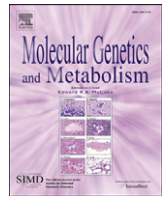




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## Carnitine palmitoyltransferase 1A (CPT1A) P479L prevalence in live newborns in Yukon, Northwest Territories, and Nunavut

Sorcha A. Collins<sup>a</sup>, Graham Sinclair<sup>b</sup>, Sarah McIntosh<sup>a</sup>, Fiona Bamforth<sup>c</sup>, Robert Thompson<sup>d</sup>, Isaac Sobol<sup>e</sup>, Geraldine Osborne<sup>e</sup>, Andre Corriveau<sup>f</sup>, Maria Santos<sup>f</sup>, Brendan Hanley<sup>g</sup>, Cheryl R. Greenberg<sup>h</sup>, Hilary Vallance<sup>b</sup>, Laura Arbour<sup>a,\*</sup>

<sup>a</sup> Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada

<sup>b</sup> Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada

<sup>c</sup> Department of Laboratory Medicine and Pathology, University of Alberta Hospital, Edmonton, Alberta, Canada

<sup>d</sup> Cadham Provincial Laboratory, University of Manitoba, Winnipeg, Manitoba, Canada

<sup>e</sup> Health and Social Services, Government of Nunavut, Iqaluit, Nunavut, Canada

<sup>f</sup> Department of Health and Social Services, Government of Northwest Territories, Yellowknife, Northwest Territories, Canada

<sup>g</sup> Health and Social Services, Government of Yukon, Whitehorse, Yukon, Canada

<sup>h</sup> Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada

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### ABSTRACT

Carnitine palmitoyltransferase 1A (CPT1A), encoded by the gene *CPT1A*, is the hepatic isoform of CPT1 and is a major regulatory point in long-chain fatty acid oxidation. CPT1A deficiency confers risk for hypoketotic hypoglycaemia, hepatic encephalopathy, seizures, and sudden unexpected death in infancy (SUDI). It remains controversial whether the *CPT1A* gene variant, c.1436C>T (p.P479L), identified in Inuit, First Nations, and Alaska Native infants, causes susceptibility to decompensation, in particular during times of fever and intercurrent illness. Although newborn screening for the P479L variant occurs in some jurisdictions, background knowledge about the presence of the variant in Canadian Aboriginal populations is lacking. In an effort to understand the population implications of the variant in northern Canada, overall frequencies of the variant were assessed. Further studies are underway to determine associated risk. Ethics approval was obtained from university REBs, local research institutes, and with consultation with territorial Aboriginal groups. Newborn screening blood spots from all infants born in 2006 in the three territories were genotyped for the p.P479L variant. p.P479L (c.1436C>T) allele frequencies in the three territories were 0.02, 0.08, and 0.77 in Yukon ( $n = 325$ ), Northwest Territories ( $n = 564$ ), and Nunavut ( $n = 695$ ), respectively. Homozygosity rates were 0%, 3%, and 64%. Aboriginal status was available only in NWT, with allele frequencies of 0.04, 0.44, 0.00, and 0.01 for First Nations, Inuvialuit/Inuit, Métis, and non-Aboriginal populations. Although individual blood spots were not identified for Aboriginal ethnicity in Nunavut infants, ~90% of infants in Nunavut are born to Inuit women. The allele frequency and rate of homozygosity for the CPT1A P479L variant were high in Inuit and Inuvialuit who reside in northern coastal regions. The variant is present at a low frequency in First Nations populations, who reside in areas less coastal than the Inuit or Inuvialuit in the two western territories. The significance of the population and geographic distribution remains unclear, but the high population frequencies of the variant suggest a historically low penetrance for adverse outcomes. Further evidence is needed to determine if there is an increased risk for infant mortality and morbidity and whether newborn screening will be indicated on a population basis.

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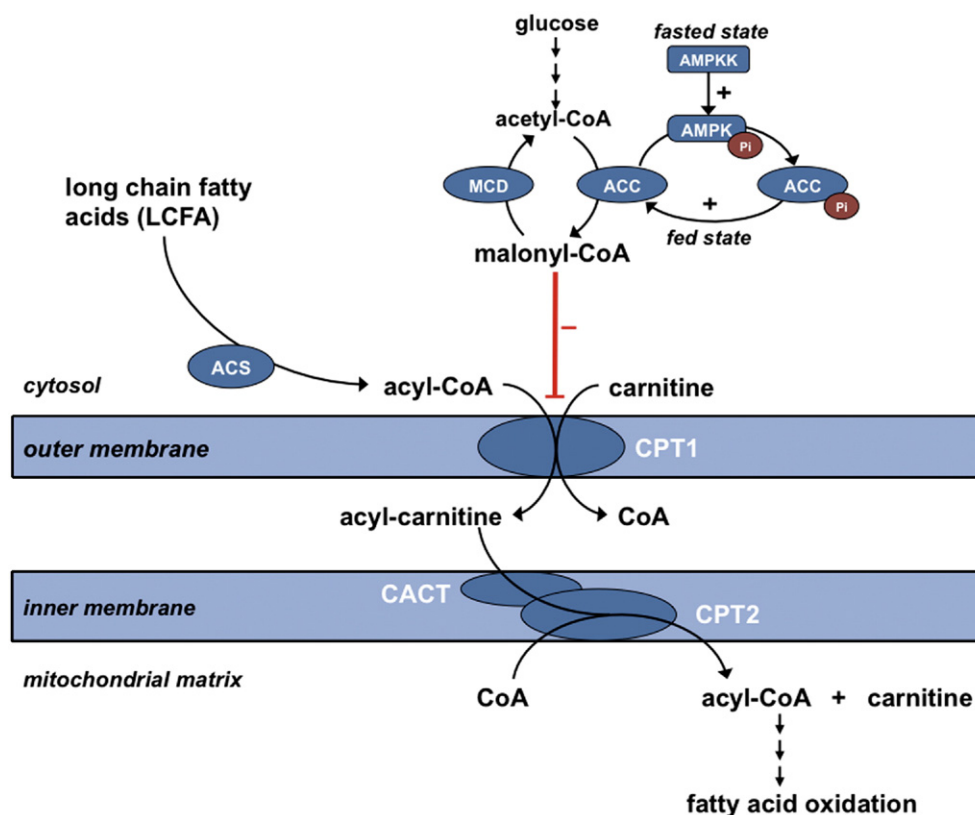
### 1. Introduction

First reported in 1981, classic carnitine palmitoyltransferase 1A (CPT1A) deficiency is a rare autosomal recessive disorder that confers risk for hypoketotic hypoglycaemia, hepatic encephalopathy, seizures, and sudden unexpected death in infancy (SUDI) [1–4]. The CPT1 enzyme is located on the outer mitochondrial membrane and is required for the import of long-chain fats into the mitochondria for use in fatty acid oxidation (Fig. 1) [1–3,5]. *CPT1A* encodes the liver isoform of CPT1; the other two isoforms are CPT1B (heart and muscle) and CPT1C (brain)

**Abbreviations:** CPT1A, carnitine palmitoyltransferase 1A; SIDS, sudden infant death syndrome; SUDI, sudden unexpected death in infancy.

\* Corresponding author. UBC Department of Medical Genetics, Medical Sciences Building, University of Victoria, PO Box 1700, STN CSC, Victoria, British Columbia, Canada V8P 5C2. Fax: +1 250 472 4283.

E-mail address: [larbour@uvic.ca](mailto:larbour@uvic.ca) (L. Arbour).



**Fig. 1.** Carnitine palmitoyltransferase pathway. During the fed state, ACC is active and converts the glucose product acetyl-CoA into malonyl-CoA. Accumulation of malonyl-CoA inhibits CPT1 activity. During fasting, glucagon signals activation of AMPKK, which triggers the deactivation of ACC via phosphorylation. Malonyl-CoA levels drop and CPT1 is released from inhibition. CPT1 exchanges the CoA molecule for carnitine on long-chain fatty acyl-CoA, which is then shuttled across the mitochondrial intermembrane space to the inner membrane by CACT. CPT2 reverses the CPT1 reaction. Free carnitine returns to the cellular cytoplasm and fatty acyl-CoA is transported into the mitochondria for fatty acid oxidation [1–3,5]. ACC, acetyl-CoA carboxylase; ACS, acyl-CoA synthetase; AMPK, AMP-activated protein kinase; AMPKK, AMP-activated protein kinase kinase; CPT1, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; CACT, carnitine translocase; MCD, malonyl-CoA decarboxylase.

[5,6]. Those homozygous for a thermolabile variant of CPT1A, p.P479L (c.1436C>T), have decreased CPT1A activity (2–54% of normal with a mean of 22%), and may be at risk of decompensation during times of fever and intercurrent illness [7–9]. Several Nunavut Inuit and British Columbia (BC) First Nations infants and children have presented symptomatically with features consistent with CPT1A deficiency or with sudden unexpected death and were subsequently found to be homozygous for the P479L variant [9–12]. However, population studies of the P479L variant have not yet confirmed whether the variant is contributing to the adverse outcomes observed, or if it is simply associated due to the high P479L frequency in these populations. All those presenting with apparent clinical features to date have been reported in First Nations and Inuit children [9–12].

Classic CPT1A deficiency is normally detectable through newborn screening by analysing levels of free carnitine over acylcarnitine profiles (C16 + C18) using tandem mass spectrometry [13]. Although this standard method has been used to identify a number of Alaskan infants with abnormal acylcarnitine profiles, not all infants homozygous for the P479L variant are identified using the standard cut off values and many infants homozygous for the variant are asymptomatic [9,10,14]. Targeted genotyping of CPT1A has been a routine component of expanded newborn screening in Manitoba targeted only to Hutterite newborns with classical CPT1A deficiency, where the disease causing mutation (c.2129G→A; p.G710E) is prevalent (homozygosity rate of ~1/400) and is associated with severe disease [4]. Whether a similar DNA-based expanded newborn screening should be instituted for those newborns at risk for adverse outcomes due to the CPT1A P479L variant remains to be determined. Previous reports have suggested that the P479L variant is surprisingly frequent in the Inuit of the Kivalliq region of Nunavut and the Inuit of Greenland (81% and 73%,

respectively) [9,15]. To date, screening for the variant in the three territories has not yet been implemented since there is controversy as to whether P479L homozygosity confers risk for infant morbidity and mortality. For that reason, an evidence based process was initiated to determine the population implications of the variant in the three northern territories where 50% of the inhabitants are Aboriginal (25% in Yukon, 50% in Northwest Territories (NWT), and 86% in Nunavut) [16].

Of particular concern, infant mortality rates (IMR) in the three Canadian territories are 1.3–3 times the national average. Nunavut has the highest infant rate in Canada at 15 per 1,000 live births [17] and has the largest Inuit population in Canada [16]. The leading cause of infant mortality in Inuit inhabited areas of Canada is Sudden Infant Death Syndrome/Sudden Unexpected Death in Infancy (SIDS/SUDI), with a rate more than 7 times the national average [18]. Risk factors for SIDS and SUDI may include undiagnosed metabolic disorders, which are considered to account for 3–6% of SIDS and SUDI cases in all populations [19,20].

We present the results of our background study to determine the allele frequency across Canada's North. The results of this study will be combined with results from a concurrent study of P479L frequency in infant mortality cases in the three territories to provide an assessment as to whether newborn screening or other public health measures should be considered.

## 2. Methods

### 2.1. Ethics

Ethics and regulatory approval was obtained from UBC Research Ethics Board, Aurora Research Institute (NWT), Stanton Territorial

Health Authority (NWT), Nunavut Research Institute, and the University of Manitoba. Territorial Aboriginal organisations consultation included: Nunavut Tunngavik Inc. (NTI), the Inuvialuit Regional Corporation (NWT), the Dene Nation (NWT), and the Yukon First Nations Health Commission.

## 2.2. Sample collection

In collaboration with the Newborn Screening program at the BC Children's Hospital, the Alberta Newborn Screening Program, and the Newborn Screening program at the Cadham Provincial Laboratory in Manitoba, newborn dried blood spots (DBS) were collected for infants born in 2006 in the Yukon, NWT, and Nunavut and were genotyped for the p.P479L variant of CPT1A. Due to samples not being available prior to April 2006 from the Baffin Island region, spots from a full calendar year from April 6, 2006 to March 30, 2007 were tested. The DBS cards were identified and accessed from storage based on patient health identification number, location of birth, or mother's place of residence. All samples were anonymized and provided with a unique identifier. Individual Aboriginal identity according to genotype could be determined for samples from NWT, where the maternal health number is informative for First Nations, Inuvialuit, Métis, and non-Aboriginal ancestry. This method should identify all Aboriginal residents receiving benefits allocated to Aboriginal groups in NWT; however, there may be some Aboriginal individuals not identified as such by their health care number and, in some rare cases, individuals identified as Aboriginal by their health care numbers who are not ethnically Aboriginal.

## 2.3. Genotype analysis

DNA was extracted from 3 mm bloodspot punches using the Genra Generation Capture Kit following the manufacture's protocol (Qiagen, Mississauga, Ont.). Genotyping of the Kivalliq region samples was conducted using the PCR-RFLP technique, as previously described [9]. All other samples were genotyped using TaqMan allelic discrimination RT-PCR assay. DNA was amplified by PCR using a 25 µl reaction mixture containing: 2.5 µl of purified DNA, 12.5µl TaqMan Universal PCR Master Mix (Applied Biosystems, Mississauga, ON), 9.375 µl of dH<sub>2</sub>O, and 0.625µl CPT1A Probe and Primer Mix "CPT1a-CPT1, SNP Abd" (containing primers: GGCCTCAACGCTGAACACT (5'); GTGAAAACCTCACCTCCCAAAGGT (3'); normal reported: CPT1A-CPT1V2, CACGATCGGCGCATC, VIC; mutant reporter: CPT1A-CPT1M2, CACGATCAGCGCATC). PCR amplification was conducted using a PRISM 7000 sequence detection system (Applied Biosystems). Reaction conditions were 2 min at 50 °C, 10 min at 95 °C, followed by 40 thermal cycles of 15 s at 95 °C and 1 min at 60 °C. Sample genotype was determined using the ABI Prism 7000 SDS software by analysing the allelic specific fluorescence data.

## 2.4. Statistical analysis

Genotype frequencies were calculated and statistically analyzed using the  $\chi^2$  test to analyse deviation from predicted frequencies from the Hardy-Weinberg equation with  $p < 0.05$  significance level. Hardy-Weinberg equilibrium (HWE) analysis was carried out in Aboriginal specific populations when possible.

## 3. Results

The P479L variant genotype frequencies, shown in Table 1, varied throughout Canada's North. The highest prevalence was in Nunavut, where the overall territorial P479L allele frequency for infants born in 2006 was 0.77 (95%CI: 0.75–0.79). The allele frequency varied in the three Nunavut regions, with the Kitikmeot

**Table 1**

Distribution of CPT1A P479L genotypes with estimated allele frequencies in infants born in 2006 in the Northern territories of Canada.

	n	wt/wt <sup>a</sup>		wt/P479L		P479L/P479L		P479L allele	
		n	f	n	f	n	f	f	95% CI
Nunavut	695	67	0.10	186	0.27	442	0.64	0.77 <sup>b</sup>	0.75–0.79
Baffin Island	302	51	0.17	89	0.30	162	0.54	0.68 <sup>b</sup>	0.64–0.72
Kivalliq	243	11	0.05	62	0.26	170	0.70	0.83	0.80–0.86
Kitikmeot	150	5	0.03	35	0.23	110	0.73	0.85	0.81–0.89
NWT	564	494	0.88	52	0.09	18	0.03	0.08 <sup>b</sup>	0.06–0.10
Inuit/Inuvialuit	70	23	0.33	32	0.46	15	0.21	0.44	0.36–0.52
First Nations	233	216	0.93	14	0.06	3	0.01	0.04 <sup>b</sup>	0.02–0.06
Métis	31	31	1.00	0	0.00	0	0.00	0.00	–
Non-Aboriginal	227	221	0.97	6	0.03	0	0.00	0.01	0.00–0.02
undefined	3	3	1.00	0	0.00	0	0.00	0.00	–
Yukon	325	312	0.96	13	0.04	0	0.00	0.02	0.01–0.03

<sup>a</sup> Wild type.

<sup>b</sup> Genotype frequencies deviated from HWE ( $p < 0.05$ ).

region having the highest (0.85; 95%CI: 0.81–0.89), followed by Kivalliq (0.83; 95%CI: 0.80–0.86), and Baffin Island (0.68; 95%CI: 0.64–0.72). The P479L variant deviated from HWE ( $p < 0.001$ ) in the Baffin Island region. Aboriginal status was not available for the Nunavut DBS samples, however, ~90% of births are to Inuit women, or approximately 272 of the 302 infants born in 2006 in Baffin Island [18]. If all heterozygotes and homozygotes in the Baffin Island region were of Inuit ancestry, the allele frequency would be 0.76 in this reduced sample, which is not statistically different than the other regions, and results in an allele distribution that is within HWE ( $p > 0.05$ ).

In NWT, the territorial allele frequency was substantially lower than in Nunavut, at 0.08 (95%CI: 0.06–0.10). The Inuvialuit had the highest frequency (0.44; 95%CI: 0.36–0.52), followed by First Nations (0.04; 95%CI: 0.02–0.06). There were 6 heterozygotes in the non-Aboriginal group. The P479L variant was not detected in those with maternal self-identification as Métis ( $n = 31$ ). The P479L allele distribution in the Inuvialuit was within HWE.

In the Yukon, there were no P479L allele homozygotes but 13 heterozygotes. Since Aboriginal status was not available for Yukon DBS samples, it was not possible to determine if all heterozygous infants were of Aboriginal ancestry. In 2006, 21.7% ( $n = 71$ ) of Yukon births were to Status Indian mothers. If all 13 heterozygotes were Aboriginal, this would result in an allele frequency of 0.09 in the Aboriginal population (carrier rate of 1/6).

## 4. Discussion

Hepatic CPT1A imports long-chain fatty acids into mitochondria for use in fatty acid oxidation (Fig. 1) [1–3,5]. CPT1A is active during fasting to maintain energy and blood glucose levels. In the fed state, CPT1A is inhibited by malonyl-CoA, a product of glycolysis and substrate of fatty acid synthesis. Classic CPT1A deficiency is a rare autosomal recessive disorder and presents in infancy with hypoketotic hypoglycemia, seizures, hepatoencephalopathy, and sudden death, if not treated [1–3].

A CPT1A variant, p.P479L (c.1436C>T), is present in Canadian and Greenland Inuit, BC First Nations, and Alaska Natives [9,10,15]. The P479L variant was first characterised in an adult First Nations male with an adult-onset metabolic disorder which included muscle cramping and occasional loss of consciousness, however the association of his disease symptoms with the variant have become less clear over time [7]. In vitro, the P479L variant protein is constitutively active due to the reduced inhibition by malonyl-CoA and has decreased thermostability and functional activity (<50%) [7,9]. Although the pathogenic link between the variant and infant mortality and morbidity has not yet been established, it may



confer risk when combined with secondary exogenous stressors, i.e. fever and illness. A number of Inuit and BC First Nations children, all homozygous for the allele, have presented with clinical features such as hypoglycaemia, seizures, and sudden unexpected death; symptoms that are consistent with a condition of impaired fatty acid oxidation [9,10]. Autopsy findings of infants homozygous for the allele have included fatty infiltrates into the liver and, in one case, into the right ventricle (unpublished data). A study of the Kivalliq region of Nunavut found that 70% of infants who died unexpectedly during the study period were homozygous for the P479L variant [9]. Since the allele frequency was high in the region and the number of deaths during the study period was very small, statistical significance for increased risk of mortality was not reached.

This study suggests a high frequency of the P479L variant in Nunavut and Inuit/Inuvialuit infants born in 2006, which is consistent with results from previous studies of Inuit populations in the Kivalliq region of Nunavut and in Greenland [9,15]. The allele distribution was not consistent with HWE ( $p < 0.001$ ) in Nunavut as a whole, but this may not be true within the Inuit population of this region. If it is assumed that all P479L homozygotes and heterozygotes are of Inuit ancestry, the allele distribution does not significantly deviate from HWE within this subpopulation. Although approximately 90% of infants born in Nunavut are born to Inuit women, this proportion does not include infants with Inuit fathers and non-Inuit Mothers [18], so the value of 90% may be under-representing the proportion of infants born in Nunavut with at least one Inuit parent. Calculations of HWE are not likely helpful here without complete ancestry information.

The P479L allele frequency in the Inuvialuit of NWT (21% homozygosity) was markedly lower than in the Nunavut Inuit, but was similar to that estimated for Alaskan Natives (~20% homozygosity) [10]. The allele prevalence in the NWT First Nations and in the general population of Yukon was low (0.04, 0.02 respectively), with only 1% homozygosity in NWT First Nations and no homozygotes present in the Yukon during our study. The low homozygosity in these groups was unexpected since it is estimated that ~20% of BC First Nations are homozygous for the allele [12]. If all P479L carriers detected in the Yukon newborn blood spots are of Aboriginal ancestry, the allele frequency would 0.09 in this population. The absence of P479L allele homozygotes during the study period is within expectation for this allele frequency and sample size and, therefore, the allele distribution would remain consistent with HWE.

The high prevalence of the variant in the Inuit populations might suggest a historical benefit for those with the P479L variant in these regions. The traditional diet of populations in Canada's North was a high fat, moderate protein diet with little to no carbohydrate sources available [21]. The constitutively active, malonyl-CoA resistant, P479L CPT1A protein may have been advantageous by maintaining fatty acid oxidation and ketogenesis at all times; this would be especially advantageous during periods of diet change when high fat food sources were limited [9]. Study of plasma HDL-cholesterol and associated apoA-I in Greenland Inuit found a possible protective effect associated with the variant against cardiovascular disease in adults, although this information alone does not likely explain a selective advantage for the variant [15]. The presence of the variant in the distantly related populations of Inuit and Inuvialuit of Nunavut and NWT, the Inuit of Greenland, and the Yupik Alaskan Natives indicates that this variant may have a place in the history of these populations. The relationship of the variant in BC First Nations as a dietary advantage remains unclear, as does the ancestral relationship to Inuit populations.

Although the high prevalence of the P479L variant decreases the likelihood that homozygosity for the variant was deleterious historically, it is possible that current dietary practices, including

the consumption of carbohydrate rich foods and decreased length of breast feeding, could play a role in increasing risk for infants who might be affected with accompanying intercurrent illness [22,23]. Further study is currently underway to determine the prevalence of the P479L variant in infant mortality cases in all three territories. Results from the current study will be combined with that study to determine if the P479L variant plays a role in the excess infant mortality cases found in the Canadian Northern territories.

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