

Carnitine Palmitoyltransferase I and Sudden Unexpected Infant Death in British Columbia First Nations



WHAT'S KNOWN ON THIS SUBJECT: The *CPT1A* p.P479L variant is common to northern aboriginal populations, leads to reduced enzyme activity, and may be associated with increased infant mortality rates.



WHAT THIS STUDY ADDS: The p.P479L variant is common in British Columbia First Nations with a coastal distribution correlated with regions of high infant mortality. Homozygotes display an altered acylcarnitine profile and are overrepresented in cases of sudden unexpected infant death in these areas.

abstract

OBJECTIVE: Infant mortality in British Columbia (BC) First Nations remains elevated relative to other residents. The p.P479L (c.1436C>T) variant of carnitine palmitoyltransferase 1 (*CPT1A*) is frequent in some aboriginal populations and may be associated with increased infant deaths. This work was initiated to determine the performance of acylcarnitine profiling for detecting this variant, to determine its frequency in BC, and to determine if it is associated with sudden infant deaths in this population.

METHODS: Newborn screening cards from all BC First Nations infants in 2004 and all sudden unexpected deaths in BC First Nations infants (1999–2009) were genotyped for the *CPT1A* p.P479L variant and linked to archival acylcarnitine data.

RESULTS: The *CPT1A* p.P479L variant is frequent in BC First Nations but is not evenly distributed, with higher rates in coastal regions (up to 25% homozygosity) with historically increased infant mortality. There is also an overrepresentation of p.P479L homozygotes in unexpected infant deaths from these regions, with an odds ratio of 3.92 (95% confidence interval: 1.69–9.00). Acylcarnitine profiling will identify p.P479L homozygotes with a 94% sensitivity and specificity.

CONCLUSIONS: The *CPT1A* p.P479L variant is common to some coastal BC First Nations, and homozygosity for this variant is associated with unexpected death in infancy. The high frequency of this variant in a wide range of coastal aboriginal communities, however, suggests a selective advantage, raising the possibility that this variant may have differing impacts on health depending on the environmental or developmental context. *Pediatrics* 2012;130:e1162–e1169

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KEY WORDS

carnitine palmitoyltransferase, *CPT1A*, p.P479L, aboriginal, First Nations, British Columbia, death, acylcarnitine, variant, fatty acid

ABBREVIATIONS

BC—British Columbia
CI—confidence interval
CPT1A—carnitine palmitoyltransferase 1A
C0—free carnitine
C16—hexadecanoylcarnitine
C18—octadecanoylcarnitine
FN—First Nations

Dr Sinclair participated in all aspects of the study, including study conception and design, acquisition, analysis, and interpretation of data, and drafting and revision of the article; Ms Collins participated in the acquisition, analysis, and interpretation of data, along with revision of the article; Dr Popescu participated in the acquisition and interpretation of data, along with revision of the article; Dr McFadden participated in the acquisition and interpretation of data, along with revision of the article; Dr Arbour participated in the study design, analysis, and interpretation of the data and revision of the article; and Dr Vallance participated in the study conception and design, analysis and interpretation of data, and drafting and revision of the article.

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Infant mortality rates in British Columbia (BC) First Nations (FN) vary across the province but are as high as 14.6 per 1000 live births on Vancouver Island, >3 times the rate for other BC residents.¹ The causes for this discrepancy in health status are multifactorial, with access to health care, socioeconomic conditions, and unsafe sleeping practices all playing major roles.² Underlying biochemical and genetic factors may, however, also interact with these environmental conditions to influence the risk of death in some infants.

Carnitine palmitoyltransferase 1 (CPT1) plays a key role in the transport of fatty acids into the mitochondrion as a source of energy during periods of fasting, high energetic demand, or low carbohydrate availability. Complete deficiency in the liver isoform of CPT1 (*CPT1A*) is rare and leads to a severe neonatal-onset disorder presenting with hypoketotic hypoglycemia, a Reye-like encephalopathy, and historically, sudden death in a large proportion of cases.³ Such a defect can be detected by acylcarnitine profiling owing to an elevation in free carnitine (C0) and a deficiency in long-chain acylcarnitines (hexadecanoylcarnitine [C16] and octadecanoylcarnitine [C18] species).⁴

A homozygous variant in the *CPT1A* gene (c.1436C>T, p.P479L) was originally identified in an FN adult and a number of Inuit individuals with symptoms suggestive of a disorder of fatty acid oxidation.^{5–8} Subsequently, however, this variant has been found to be highly prevalent in aboriginal communities across the north, including Greenland, Nunavut, Northwest Territories, and Alaska.^{9–11} In BC, homozygosity for the p.P479L variant was identified in a series of FN infants who died unexpectedly and also in their asymptomatic siblings and parents. All individuals had a mildly elevated bloodspot C0/(C16 + C18) ratio. An anonymous selective

sampling study suggested a high p.P479L allele frequency in BC FN.¹²

Given the high frequency of this variant in these populations and the fact that most homozygotes remain asymptomatic, the clinical significance of this variant has remained unclear. In vitro testing confirmed a reduction in CPT1 activity in p.P479L homozygous fibroblasts (2%–22% of control mean) and heterologous expression studies (50% of controls), with a simultaneous reduced response to malonyl-coenzyme A inhibition (a major regulator of hepatic CPT1 activity).^{5,6} Given the elevated risk of sudden unexpected death in some BC FN individuals and the presence of this variant in the same populations, this study was initiated to determine if bloodspot acylcarnitine profiling was sensitive for the detection of p.P479L homozygosity, to establish the underlying frequency of the variant in BC, and to determine if homozygosity for the variant is associated with an increased risk of sudden unexpected infant death in these populations.

METHODS

Ethics

This study was motivated by the identification of a potential public health concern in BC FN communities. Accordingly, consultation was undertaken with BC First Nations Chief's Health Council, FN and Inuit Health Branch of Health Canada, and BC Ministry of Health. The Tripartite Committee on FN's Health granted approval for access to required BC Vital Statistics data and stored newborn screening bloodspot cards. This committee also participated in a review of the study results. Institutional ethics approval was obtained from both the Children's and Women's Health Centre of BC research review board and the University of British Columbia clinical research ethics board.

Population Data

The BC Vital Statistics birth registry was queried for self-declaration of aboriginal heritage (either mother or father) for all births in 2004 and matched to stored newborn screening cards (2332 samples). All data were de-identified and included only a specimen number for the stored card and the first 3 digits of the mother's postal code (Forward Sortation Area). By using this specimen number, all samples were genotyped for the p.P479L variant and matched to stored acylcarnitine profile data that were previously generated as part of the routine newborn screening process. Comparison with FN infant mortality rates was performed by matching the Health Service Delivery Area (reporting region for infant deaths) to the Forward Sortation Area for each sample by using the links available from the BC Vital Statistics Translation Master File (extract available at: http://www.bcstats.gov.bc.ca/data/pop/georef/place_names.xls).

Sudden Death Cases

The BC Coroners Service requires an autopsy to be performed at BC Children's Hospital for all infant deaths (<2 years of age) considered to be natural, sudden and unexpected, or unknown. All coroner's autopsy cases at BC Children's Hospital from 1999–2009 were reviewed, and 51 cases were identified with a known FN heritage and no clear anatomic or toxicological cause of death. All 51 cases were genotyped for the p.P479L variant by using a post-mortem bloodspot sample routinely collected at autopsy or an original newborn screening card, if available. These cases also were stratified by postal code data into the regional clusters defined by the 2004 population data. All samples with an available newborn screening card were matched to the stored acylcarnitine profile data generated at the original time of screening.

Acylcarnitine data were available from 2003 forward.

Acylcarnitine Profiling

Acylcarnitine profiles were produced from dried bloodspot samples as butyl-derivatives, as previously described.¹³ Briefly, acylcarnitines were extracted from 3-mm punches of the dried bloodspots in 400 μ L of 100% methanol containing appropriate stable-isotope internal standards. A set of dried bloodspot external calibrators, prepared for all major acylcarnitine species, was analyzed in each batch, and individual recoveries were corrected by the slope of the calibration curve. All minor species were corrected by using the slope from a major species of similar mass. Extracted acylcarnitines were evaporated to dryness and butylated using butanolic-HCl for 15 minutes at 60°C. Samples were again evaporated to dryness and resuspended in 400 μ L of mobile phase (80:20 acetonitrile:distilled deionized water with 10 mM of ammonium formate). Twenty-five microliters of this derivitized extract was injected for analysis by flow injection tandem mass spectrometry by utilizing a Waters Quattro Micro tandem mass spectrometer and multiple reaction-monitoring data acquisition (Waters LTD, Mississauga, Ontario). Owing to age-specific changes in acylcarnitine values, all data are presented only from initial newborn bloodspot samples (collected within 7 days of birth).

Genotyping

DNA was extracted from 3-mm dried bloodspot punches by using the Gentra Generation DNA extraction and DNA purification solutions according to the manufacturer's directions (Qiagen Inc, Mississauga, Ontario). The c.1436C>T (p.P479L) variant was assayed by using a custom-designed Taqman Allelic Discrimination Assay on an ABI 7000 Real-Time

PCR (polymerase chain reaction) instrument (Life Technologies, Carlsbad, CA), as previously described.⁹

SaTScan Analysis

Because population stratification can be a major confounder in genetic association studies, geographical clustering of p.P479L allele frequency was analyzed by using SaTScan version 8.0 (M. Kulldorff and Information Management Services, Inc, www.satscan.org). p.P479L homozygote counts were compared with the total population by using the geographical center of the Forward Sortation Area (postal code) as the geographical locator. The data were scanned by using a purely spatial discreet Poisson model for high- and low-frequency clusters, allowing overlap between the clusters.

RESULTS

Acylcarnitine Profiling

To determine the performance of bloodspot acylcarnitine profiling for the detection of homozygosity for the

p.P479L variant, acylcarnitine profiles for the 2332 FN samples in the 2004 birth year were designated as cases (p.P479L homozygotes) or controls (p.P479L heterozygotes and wild type) and subjected to receiver operating characteristic curve analysis for all individual acylcarnitines and a number of acylcarnitine ratios (Analyze-IT Software LTD, Leeds, United Kingdom). The highest-performing tests are depicted in Fig 1. As suggested by previous studies, the C0/(C16+C18) ratio was among the highest-performing parameters, with a 94% sensitivity and a 94% specificity for the detection of p.P479L homozygotes at an optimal cutoff of 14. Other ratios of C0 to various long-chain acylcarnitines were equally effective, although C0 alone showed reduced performance (Fig 1).

A comparison of the C0/(C16+C18) ratio between non-FN births (all BC births in 2004 excluding the FN births, $n = 39\,709$) and FN newborns not carrying the p.P479L variant showed no significant differences (Fig 2). Homozygotes for p.P479L, however, did show a significant increase in the C0/(C16+C18) ratio, as

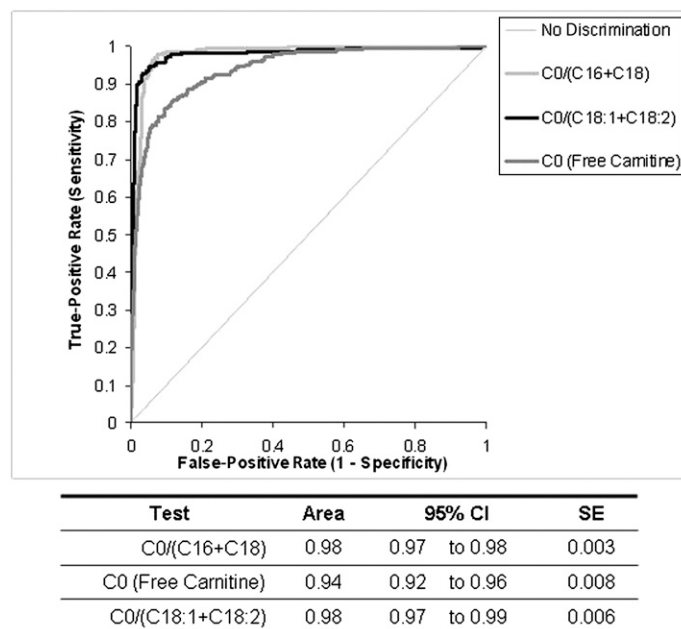


FIGURE 1

Receiver operating characteristic curves for the detection of p.P479L homozygosity based on newborn bloodspot acylcarnitine profiles. The analysis is based on genotyping data for FN births in 2004 ($n = 2332$), including 225 p.P479L homozygotes.

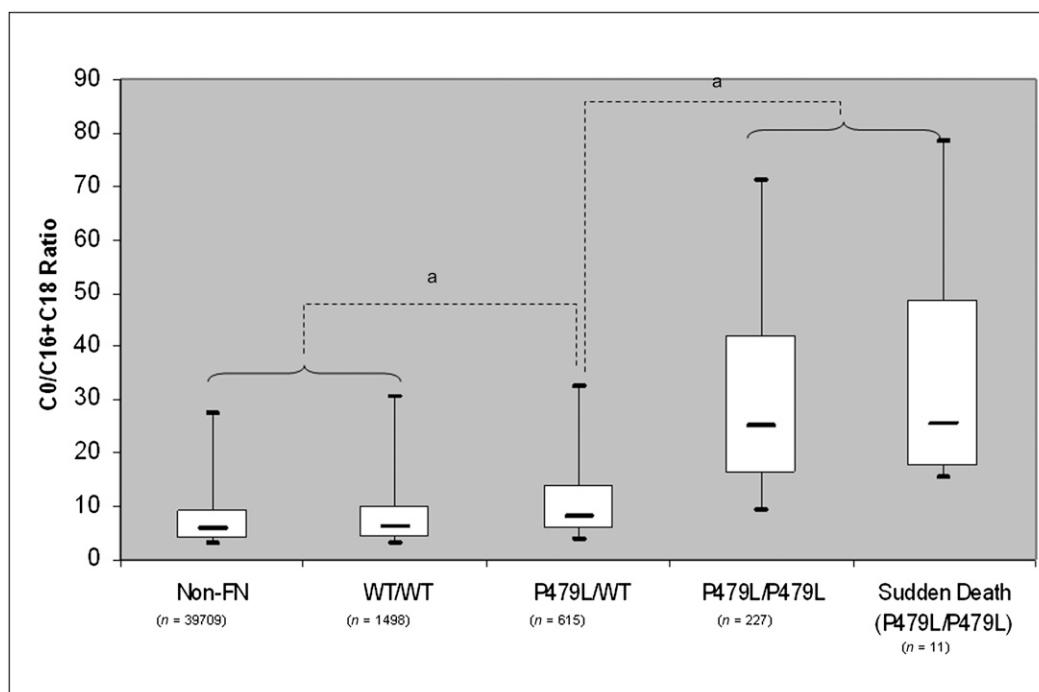


FIGURE 2

The newborn bloodspot C0/(C16+C18) ratio for non-FN births (non-FN), FN births, stratified by *CPT1A* genotype (WT/WT, P479L/WT, and P479L/P479L), and homozygous FN sudden death cases (1999–2009).^a Mean values were significantly different by 1-way analysis of variance ($P < .0001$) with pair-wise comparisons (Schaefe) showing significant differences between, but not within, the genotype groups. The boxes represent the 10th to 90th percentiles, with the interior line depicting the 50th percentile. Vertical lines extend to the first and 99th percentiles. WT, wildtype.

predicted. Interestingly, p.P479L heterozygotes also showed a small but significant increase in this ratio, suggesting a minor functional decrease in overall CPT1 activity. Comparison of the C0/(C16+C18) ratio between p.P479L homozygotes from the 2004 birth year and sudden death cases did not reveal any significant differences, suggesting that acylcarnitine profiling is not a useful prognostic tool in the immediate neonatal period (Fig 2).

Population Genotyping

Genotyping results from the 2004 birth year showed a high frequency of the p.P479L allele in BC, with 9.8% of all FN newborns homozygous for the variant (Fig 3). A comparison of genotype frequencies showed that the p.P479L allele is not in the Hardy-Weinberg Equilibrium, and accordingly, all subsequent analysis compared genotype rather than allele frequencies (data

not shown). A similar deviation from Hardy-Weinberg Equilibrium also has been reported for the p.P479L allele for some of the populations tested in Alaska, the Northwest Territories, and Nunavut.^{9,10} It was clear from the postal code data that the frequency of the variant was not uniform across the province, and a spatial clustering approach was used to define statistically significant clusters of uniform p.P479L homozygosity. As seen in Fig 3, this analysis defined 3 significant overlapping coastal clusters with comparatively high rates of p.P479L homozygosity and 2 significant regions of decreased p.P479L homozygosity. Homozygosity rates were highest in cluster 1 (Southern Vancouver Island), with >25% of births homozygous p.P479L. This finding is in contrast to the Southern Interior cluster (cluster 4, Fig 3), where only 4.3% of newborns were homozygous. All subsequent analyses limited genotype frequency comparisons

to samples with postal codes within these clusters. Infant mortality rates are increased for BC FN in comparison with other residents, with the highest rates on central and southern Vancouver Island, correlating with regions of increased p.P479L homozygosity (Fig 4).¹

Sudden Death Cases

All infant deaths (<2 years of age) classified by the BC Coroners Service as natural, sudden and unexpected, or unexplained have an autopsy performed at BC Children's Hospital. All such coroner cases from 1999–2009 were reviewed, and those with no clear anatomic or toxicological cause of death and an FN heritage were genotyped for the p.P479L variant. These cases also were stratified by postal code data into the regional clusters defined by the 2004 population data. Table 1 depicts the comparison of p.P479L homozygosity rates for sudden death

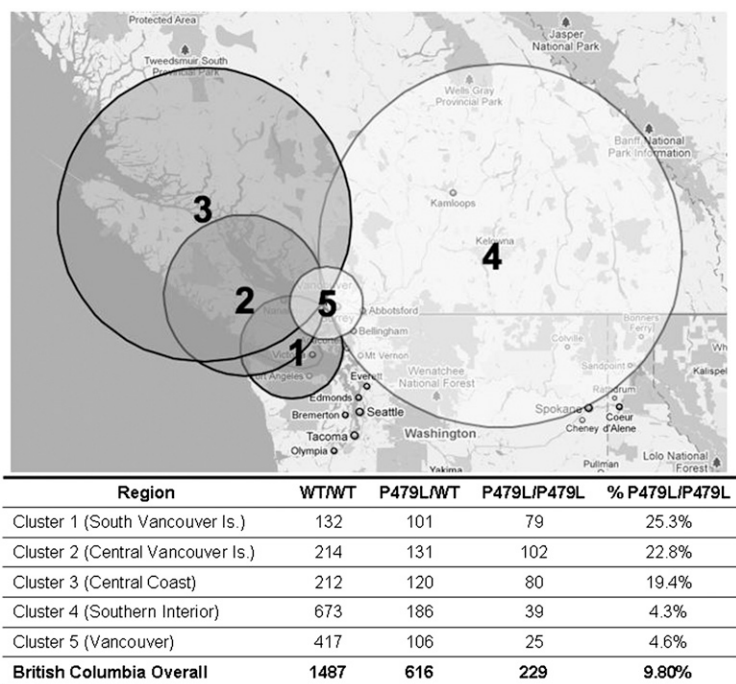


FIGURE 3 Genotype frequencies for the *CPT1A* p.P479L variant for BC FN births in the 2004 birth year ($n = 2332$). SaTScan was used to define significant clusters of uniform genotype frequency ($P > .001$).

cases as compared with the underlying FN population rate within the high-frequency clusters. The odds ratio for sudden unexpected death in p.P479L homozygotes for cluster 1 (Southern Vancouver Island) was 1.64 (95% confidence interval [CI]: 0.42–5.63; Fisher's exact test $P = .55$) and for cluster 2 (Central Vancouver Island) was 4.51 (95% CI: 1.59–13.26; Fisher's exact test $P = .014$). There were no sudden death cases in cluster 3 for this time period. Taking all 3 high-frequency clusters together, the odds ratio was significant at 3.92 (95% CI: 1.69–9.00; Fisher's exact test $P = .006$). The population-attributable risk associated with homozygosity for the p.P479L variant is also elevated, as presented in Table 1.

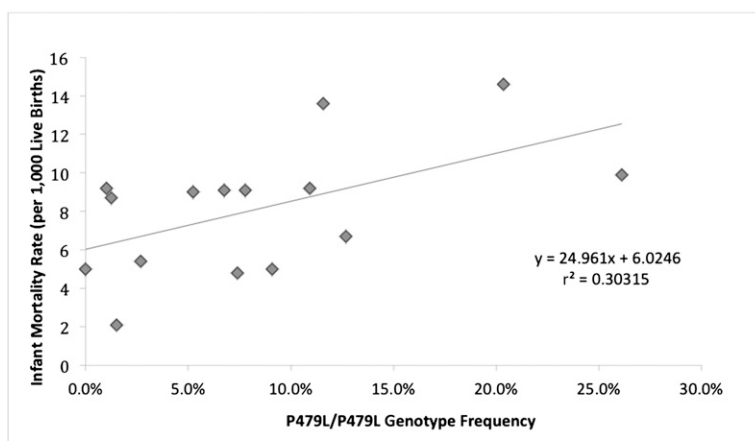
DISCUSSION

CPT 1 is a central enzyme in the mitochondrial oxidation of long-chain fatty acids and plays a key role in the regulation of β -oxidation in response to

systemic signals of energy availability. Profound deficiency in liver CPT1 (*CPT1A*) activity is known to cause a severe early-onset disorder with a high risk of infantile mortality. The *CPT1A* p.P479L variant, however, has demonstrated only a partial deficiency in enzyme activity (50%–80% reduction) in both fibroblasts and heterologous expression studies.^{5,6} Recent studies also have shown a high frequency for this variant in a number of coastal North American aboriginal populations, with p.P479L allele frequencies of 0.44 to 0.85 in Canadian Inuit communities in the Northwest Territories and Nunavut,^{6,9} 0.73 in the Greenland Inuit community,¹¹ and 0.7 in some coastal Alaska Native communities.¹⁰ Although there is some preliminary evidence to suggest an association between increased rates of infant death and homozygosity for this variant, these previous studies have been limited owing to relatively small population sizes.¹⁴

The identification of the p.P479L variant in a number of children of FN descent raised the possibility that this variant also may be common in BC. Although not evenly distributed across the province, the p.P479L allele frequency is increased in coastal BC, with maximal rates of homozygosity (25%) corresponding with historical regions of highest infant mortality. Homozygotes for p.P479L are also statistically over-represented in cases of sudden unexpected death (<2 years of age), with an odds ratio of 3.92 (95% CI: 1.69–9.00) for all high-homozygosity clusters combined. Although these data support an association between p.P479L homozygosity and sudden unexpected death in infancy, other risk factors such as prenatal maternal smoking, sleep position, and intercurrent illness were not evaluated and are likely to contribute to the circumstances that make a particular infant vulnerable.

A high underlying allele frequency and association with an increased risk of sudden unexpected death suggest this variant as a potential target for population-wide newborn screening. Given that sudden unexpected death is manifested in only a small proportion of p.P479L homozygotes (~1%) and the remainder of the clinical spectrum is poorly defined, however, the validity of newborn screening is not yet established. With appropriately defined screening cutoffs, a 94% sensitivity for p.P479L homozygosity is attainable by acylcarnitine profiling alone; however, at this level of sensitivity, the specificity remains unacceptably low, with a 6% false-positive rate for the best-performing test. A community-based public and primary care provider education program focused on reducing risk for infant mortality in general, including the potential risk associated with this common variant, may be more appropriate than a traditional newborn screening model that might



Health Service Delivery Areas	P479L/P479L, %	Infant Mortality/1000
INTERIOR		
East Kootenay	0.0	7.5
Kootenay Boundary	9.1	7.5
Okanagan	1.2	4.4
Thompson Cariboo Shuswap	7.8	6
Northwest	12.7	6.8
Northern Interior	5.2	6.5
North East	1.5	7.4
LOWER MAINLAND		
Fraser East	7.4	6.9
Fraser North	2.7	7.1
Fraser South	1.0	5.8
Vancouver	10.9	11.2
CENTRAL COAST		
North Shore/Coast Garibaldi	6.8	7.5
North Vancouver Island	11.6	15
SOUTH VANCOUVER ISLAND		
	20.4	10.1
CENTRAL VANCOUVER ISLAND		
	26.1	14.9

FIGURE 4

Correlation of the *CPT1A* p.P479L homozygosity rate with FN infant mortality rate (2002–2006) based on Health Service Delivery Area.¹ Linear regression ($y = 24.96 + 56.02x$), $r^2 = 0.3$.

focus on dietary intervention and intercurrent illness management alone. Such a public health–based approach would have the added benefit of addressing other known risk factors that might interact with homozygosity of the variant, increasing risk for sudden unexpected death.² Alternatively, a 2-tiered screening approach, including a molecular-testing step for

the p.P479L variant, could be considered; however, evaluation would be necessary for any program put in place to ensure effectiveness. Further community consultation is required to determine if newborn screening for the p.P479L variant is wanted, warranted, or feasible.

The *CPT1A* p.P479L variant has, to date, been identified only in aboriginal

populations indigenous to western and northern North America, mostly of coastal distribution. This includes coastal BC FN, Alaska Natives, Canadian Inuit, and Greenland Inuit populations. Interestingly, the allele frequency has been comparatively lower in non-coastal FN populations in BC and the Yukon.⁹ Although we show evidence that this variant is associated with sudden unexpected infant mortality, the high allele frequency in these distantly related populations appears paradoxical. Such an elevation of a single variant could reflect a simple founder effect or small population dynamics; however, the elevation of the *CPT1A* variant across such a wide geographical region and such distantly related aboriginal groups makes this etiology less likely. Alternatively, there could be a conditionally selective advantage to this variant. A number of authors have speculated or presented preliminary evidence to suggest that the p.P479L variant may represent an adaptation to the high proportion of fat (up to 85% of total calories) or distribution of long-chain fatty acids (primarily marine fats) in a traditional coastal diet.^{6,10,11,15}

Alternatively, the p.P479L variant may represent an adaptation to the type of fatty acids present in the traditional diet. The wild-type hepatic CPT1 enzyme displays a marked difference in its kinetic behavior toward various fatty-acid substrates and the overall proportion of fat in the diet.¹⁶ It also has been demonstrated that inhibition of

TABLE 1 Odds Ratio for the Association of P479L Homozygosity With Sudden Unexpected Death

Region	Group	WT/WT	WT/p.P479L	p.P479L/p.P479L	P479L/P479L, %	Odds Ratio	95% CI
Cluster 1 (Southern Vancouver Island)	Sudden death	5	4	5	35.7	1.64	0.42–5.63 ($P = .55$)
	2004 population	132	101	79	25.3		
Cluster 2 (Central Vancouver Island)	Sudden death	4	2	8	57.1	4.51	1.59–13.26 ($P = .014$)
	2004 population	214	131	102	22.5		
Cluster 3 (Central Coast)	Sudden death	0	0	0	NA	NA	NA
	2004 population	212	120	80	19.4		
All high clusters	Sudden death	5	6	10	47.6	3.92	1.6–9.00 ($P = .006$)
	2004 population	344	195	125	18.8		

Clusters were defined by SaTScan analysis by using postal code as the geographical locator. NA, not applicable; WT, wildtype allele.

CPT1 by malonyl-coenzyme A is profoundly influenced by dietary fatty acid composition.¹⁷ The p.P479L variant may represent a modification in substrate specificity as an adaptation toward a high-fat diet enriched in long-chain polyunsaturated fatty acids. Bates et al¹⁸ reported a significant increase in circulating levels of omega 3 and omega 6 polyunsaturated fatty acids in individuals from coastal BC FN, but only when a traditional diet was consumed. Interestingly, even when not consuming a traditional diet, participants in the Bates et al study showed markedly low circulating levels of proinflammatory arachidonic acid (20:4), suggesting a genetic basis and anti-inflammatory component to some of the altered lipid profiles observed.¹⁸ Given the evidence of altered lipoprotein composition in p.P479L homozygotes, lipid transport and metabolism may be modified at a number of points to optimize energy utilization and minimize the production of potentially detrimental

metabolites for those consuming a traditional coastal and northern diet.¹¹

Importantly, however, there have been no studies to date looking at the substrate specificity of the p.P479L variant with respect to fatty acid composition. Enzymatic studies to investigate the possibility of altered substrate specificity for the p.P479L *CPT1A* variant have the potential to not only elucidate the physiologic benefit of this variant but also the specific conditions in which this variant leads to increased clinical risks. In addition, more work is required to tease apart the complex interplay of environment, fatty acid regulation, and other genetic factors that may contribute to both the biological benefit and clinical harms associated with this *CPT1A* variant. In fact, the full range of clinical symptoms associated with this *CPT1A* variant have not been defined, and further prospective studies are clearly needed before the true balance of risks and benefits can be determined.

CONCLUSIONS

The *CPT1A* p.P479L variant is associated with sudden unexpected infant death in coastal BC FN communities. If this variant is a risk factor for sudden death, it is likely modulated by other environmental, social, and genetic factors. It also remains possible that there is a beneficial aspect to this variant, possibly as an adaptation to traditional diet or other historical environmental factors, but the preliminary nature of the available data limits the formation of firm conclusions in this regard. The ambiguity associated with this paradox raises significant barriers to information sharing with the affected communities, which is currently being addressed with community and local health care provider education. Further basic science, epidemiological study, and community involvement are required to fully address the positive and negative effects of the common variant on the health of coastal and northern aboriginal peoples.

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Carnitine Palmitoyltransferase I and Sudden Unexpected Infant Death in British Columbia First Nations

Graham B. Sinclair, Sorcha Collins, Oana Popescu, Deborah McFadden, Laura Arbour and Hilary D. Vallance

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