> Mol Genet Metab. 2009 Apr;96(4):201-7. doi: 10.1016/j.ymgme.2008.12.018. Epub 2009 Feb 13.

The paradox of the carnitine palmitoyltransferase type Ia P479L variant in Canadian Aboriginal populations

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PMID: 19217814
DOI: 10.1016/j.ymgme.2008.12.018

Abstract

Investigation of seven patients from three families suspected of a fatty acid oxidation defect showed mean CPT-I enzyme activity of 5.9+/-4.9 percent of normal controls. The families, two Inuit, one First Nation, live in areas of Canada geographically very distant from each other. The CPT1 and CPT2 genes were fully sequenced in 5 of the patients. All were homozygous for the same P479L mutation in a highly conserved region of the CPT1 gene. Two patients from the first family were also homozygous for the CPT2 F352C polymorphism in the CPT2 gene. Genotyping the patients and their family members confirmed that all seven patients were homozygous for the P479L variant allele in the CPT1 gene, as were 27 of 32 family members. Three of the seven patients and two cousins had hypoketotic hypoglycemia attributable to CPT-Ia deficiency, but adults homozygous for the variant denied hypoglycemia. We screened 422 consecutive newborns from the region of one of the Inuit families for this variant; 294 were homozygous, 103 heterozygous, and only 25 homozygous normal; thus the frequency of this variant allele is 0.81. There was an infant death in one family and at least 10 more deaths in those infants (7 homozygous, 3 heterozygous) consecutively tested for the mutation at birth. Thus there is an astonishingly high frequency of CPT1 P479L variant and, judging from the enzyme analysis in the seven patients, also CPT-I deficiency in the areas of Canada inhabited by these families. Despite the deficiency of CPT-Ia which is the major rate-limiting enzyme for long chain fatty acid oxidation, clinical effects, with few exceptions, were slight or absent. One clue to explaining this paradox is that, judging from the fatty acid oxidation studies in whole blood and fibroblasts, the low residual activity of CPT-Ia is sufficient to allow a reasonable flux through the

mitochondrial oxidation system. It is likely that the P479L variant is of ancient origin and presumably its preservation must have conveyed some advantage.

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