

THE LANCET

V677 mutation of methylenetetrahydrofolate reductase and cardiovascular disease in Canadian Inuit

Robert A Hegele, Cheri Tully, T Kue Young, Philip W Connelly

Reprinted from THE LANCET Saturday 26 April 1997
Vol. 349 No. 9060 Page 1221

V677 mutation of methylenetetrahydrofolate reductase and cardiovascular disease in Canadian Inuit

Robert A Hegele, Cheri Tully, T Kue Young, Philip W Connelly

Canadian Inuit have an age-adjusted mortality from cardiovascular disease of about 0.66 compared with the rest of Canada.¹ Although this might be due to the protective influence of the consumption of fish, there could also be a genetic resistance to cardiovascular disease in this population. A candidate factor is the V677 mutation in methylenetetrahydrofolate reductase (MTHFR), which is the key enzyme in the methylation of homocysteine.^{2,3} Homozygosity for the MTHFR V677 mutation may be a genetic risk factor for cardiovascular disease,^{2,3} especially when the diet is deficient in folate.³ The frequency of the MTHFR V677 allele in white people is 0.35 (95% CI 0.28–0.40), with a frequency of homozygotes of about 10%.⁴

We hypothesised that the low prevalence of cardiovascular disease in Canadian Inuit might be associated with a low frequency of the MTHFR V677 allele. We studied 174 unrelated healthy Inuit (mean age 38.1 [SD 15.7] years) from eight communities in the Keewatin region of the North West Territories of Canada. We found that the MTHFR V677 allele frequency was 0.061, significantly less than the 0.35 in a reference white population ($p < 0.0001$). In addition, 1.2% of Inuit were V677 homozygotes, compared with 12% of white people ($p < 0.0001$).

The lower prevalence of cardiovascular disease among Canadian Inuit may thus be associated with the low frequency of the MTHFR V677 allele in these people. The low frequency of V677 homozygotes could also mean that the Inuit are protected against a possible adverse effect of dietary folate deficiency, which is more prevalent in Canadian aboriginal people than in other Canadians.⁵ The prevalence of neurological phenotypes associated with the MTHFR V677 allele and dietary folate deficiency among Canadian aboriginal people is unknown. The low V677 allele frequency among the Inuit might have resulted from a founder effect involving ancestors who migrated into the central arctic some 900 years ago; alternatively, the low frequency might be the result of selection pressure related to the mutant's thermolability and to the cold climate of northern Canada. In any event, distinctive genetic features of the Canadian Inuit, including the low frequency of MTHFR V677, could explain their low prevalence of cardiovascular disease.

- 1 Young TK, Moffatt MEK, O'Neil JD. Cardiovascular diseases in a Canadian arctic population. *Am J Public Health* 1993; 83: 881–87.
- 2 Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* 1995; 10: 111–13.
- 3 Kluijtmans LAJ, van den Heuvel LPWJ, Boers GHJ, et al. Molecular genetic analysis in mild hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. *Am J Hum Genet* 1996; 58: 35–41.
- 4 Stevenson RE, Schwartz CE, Du Y-Z, Adams MJ Jr. Differences in methylenetetrahydrofolate reductase genotype frequencies between blacks and whites. *Am J Hum Genet* 1997; 60: 229–30.
- 5 Moffatt ME. Current status of nutritional deficiencies in Canadian aboriginal people. *Can J Physiol Pharmacol* 1995; 73: 745–58.

Department of Medicine, St Michael's Hospital and University of Toronto, Ontario, Canada M5B 1W8 (R A Hegele); and Department of Community Health Sciences, University of Manitoba, Canada