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Biochemical discrimination of heterozygotes for cystathionine β-synthase (CβS) deficiency. **M T Steen, A M Boddie, S Langley, G Cotsonis, W MacMahon, D Saxe, P P Dembure, C Kim, W D Kruger and L J Elsas II, Division of Med. Genet., Emory University School of Medicine, Atlanta, GA 30032.** Direct metabolite analyses would be a useful screen to discriminate CβS heterozygotes from non-carriers. We recently found that homocysteine-related metabolite ratios discriminated obligate heterozygotes for CβS deficiency from a control population. In the current study, samples from 55 first and second-degree relatives of probands with CβS deficiency were analyzed for total plasma homocysteine (tHcy), cysteine (tCys), folate (fol), cobalamin (B12), after fasting for 8 hours, and after 100 mg/kg methionine load (PL). Vitamin & smoking histories were obtained. Molecular genotypes were determined and compared to respective biochemical phenotypes.

Metabolite differences, between genotyped carriers (n=26) and non-carriers (n=29) were: folate, [(9.7 +/- 1.5 vs 15.6 +/- 1.9μM, p<0.02), erythrocyte folate (efol) (581 +/- 49 vs 372 +/- 48μM , p=0.004) and tHcy [(fasting) and (PL)], [(13.9 +/- 1.1versus 10.4 +/-1.0 μM, p=0.01) and (58.8 +/- 2.9 vs 34.5 +/- 1.9μM, p=0.013)]. The ratio of [tHcy / (efol X tCys)] after an oral methionine load, provided 100% discrimination of carriers from noncarriers (102 +/- 14.5 vs 30 +/- 2.3, p=0.0001), in non vitamin-takers. Smoking elevated ratios of carriers and noncarriers (159 +/- 19 vs 40 +/- 5, p=0.0002). Smoking increased the sensitivity and specificity of this ratio, and negated the confounding effects of vitamins. Conclusion: the ratio of [tHcy / (efol X tCys)] can discriminate carriers from noncarriers of CβS deficiency.

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An epidemiologic assessment of the relationship between the G985A medium chain acyl-coA dehydrogenase deficiency (MCADD) allelic variant and sudden infant death syndrome (SIDS). S.S. Wang, M.J.Khoury. Office of Genetics and Disease Prevention, Centers for Disease Control and Prevention, Atlanta, GA.

MCADD has been suggested to be a cause of SIDS. Results of the published literature regarding this association have been conflicting, especially for studies examining the association between SIDS and G985A, the most common mutation reported in MCADD. We therefore assessed all population-based studies published through 1998 that evaluated the relationship between G985A and SIDS (n=12). Using published data on the rates of SIDS and G985A in different populations and the proportion of SIDS cases with one or two G985A alleles, we applied Bayes' theorem to estimate the probability than an infant with G985A will die from SIDS. We also used Miettinen's formula to estimate the fraction of SIDS in the population that can be attributed to G985A. We derived a range of these estimates based on the literature.

Since rates for SIDS and G985A in the United States are different from those in Europe, we performed separate calculations for the two regions. In both the U.S. and Europe, the probability of SIDS among persons homozygous for the G985A allele was estimated as 1% (U.S. range 0% to 9%; European range 0% to 33%). This estimate is 14 times higher than the risk for SIDS in the U.S. population and at least 13 times higher than the risk for SIDS in the European populations assessed. In both populations, the proportion of SIDS that can be attributed to homozygosity for G985A was estimated as less than 0.1%. The probability of SIDS among infants heterozygous for the G985A allele was estimated as less than 0.1% for both the U.S. and Europe. These estimates produced risks 0.6 and at least 0.3 times that the rate of SIDS in the U.S. and Europe, respectively.

Although many of these studies are limited by potential selection bias, small sample size, and lack of stratification by racial and ethnic groups where much heterogeneity for G985A and SIDS exists, the data suggest that individuals homozygous for G985A have an increased risk for sudden infant death. Those heterozygous for G985A, however, do not have an increased risk for SIDS. Furthermore, the G985A MCADD allelic variant does not appear to account for a significant percentage of SIDS cases in either the U.S. or in Europe.