1. Title

*ALAD* Genotype and Lead Toxicity

2. Gene

The *ALAD* gene (chromosome 9q34) codes for δ-aminolevulinic acid dehydratase (ALAD), which catalyzes the asymmetric addition of two molecules of aminolevulinic acid (ALA) to form porphobilinogen -- the second step of heme synthesis.

3. Prevalence of Gene Variants

Eight *ALAD* variants have been described in the literature. Most attention has been paid to the G177C polymorphism, which yields two alleles, designated *ALAD-1* and *ALAD-2*. The *ALAD-2* allele contains a G → C transversion at position 177 of the coding region, resulting in the substitution of asparagine for lysine at amino acid 59. These two alleles determine three isozymes, designated 1-1, 1-2, and 2-2, all of which display similar activities but have different charges. The prevalence of the *ALAD-2* allele ranges from 0 to 20 percent depending on the population. Generally, Caucasians have the highest frequency of *ALAD-2* allele, with approximately 18 percent of the population being *ALAD 1-2* heterozygotes and 1 percent being 2-2 homozygotes. Some studies used hospital-based study samples, while others used samples comprised of occupationally exposed individuals with relatively high blood lead levels.

4. Disease Burden

Studies have shown relations between *ALAD* G177C genotype and several features of lead toxicity. The evidence surrounding this *ALAD* polymorphism and lead poisoning can be summarized as follows: at high levels of exposure and in comparison to *ALAD 1-1* genotype individuals, *ALAD 1-2/2-2* genotype individuals have increased blood lead levels, lower concentrations of ALA in the plasma (ALAP), lower zinc protoporphyrin levels, lower cortical bone lead concentrations, higher concentrations of trabecular (spongy) bone lead, and lower amounts of chelatable lead (1-3, 5). These differences are only clearly evident at blood lead concentrations greater than 25 µg/dL. The data also suggest that lead exposed *ALAD-1* homozygotes may be at greater risk of neurotoxicity than exposed *ALAD 1-2* individuals, as *ALAD-1* homozygotes have higher levels of ALAP. One study gave preliminary evidence that *ALAD 1-2* individuals may have better neuropsychological performance than *ALAD-1* homozygotes of similar lead exposure history (4).

5. Interactions

Schwartz et al. (5) have evaluated interactions between *ALAD* and *VDR*, which codes for the Vitamin D Receptor. *VDR* is polymorphic and evidence suggests that alone
it may influence the effect of lead exposure, but no evidence for gene-gene interaction was found.

6. Laboratory Tests

Whereas early studies used an electrophoretic technique to distinguish ALAD protein variants (due to charge differences), most studies have used a PCR-based genotyping technique in which the polymorphic site is amplified and then cleaved with the MspI restriction enzyme. The cleavage products are then visualized on an agarose gel. There is complete concordance between the genotyping and phenotyping techniques.

7. Population Testing

At this time, there is inadequate evidence to support population-based testing.

8. References


9. Internet sites

NIOSH http://www.cdc.gov/niosh/leadpg.html