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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 *Msp*I 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

1. Wetmur JG. Influence of the common human delta-aminolevulinate dehydratase polymorphism on lead body burden. Environ Health Perspect 1994;102 Suppl 3:215-9.

2. Fleming DE, Chettle DR, Wetmur JG, et al. Effect of the delta-aminolevulinate dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers. Environ Res 1998;77(1):49-61.

3. Schwartz BS, Lee BK, Stewart W, et al. delta-Aminolevulinic acid dehydratase genotype modifies four hour urinary lead excretion after oral administration of dimercaptosuccinic acid. Occup Environ Med 1997;54(4):241-6.

4. Bellinger D, Hu H, Titlebaum L, et al. Attentional correlates of dentin and bone lead levels in adolescents. Arch Environ Health 1994;49:98-105.

5. Schwartz BS, Lee B-L, Lee G-S, et al. Associations of Blood Lead, Dimercaptosuccinic Acid-Chelatable Lead, and Tibia Lead with Polymorphisms in the Vitamin D Receptor and δ-Aminolevulinic Acid Dehydratase Genes. Environ Health Perspect 2000;108(10):949-54.

9. Internet sites

OMIM http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=125270
NIOSH http://www.cdc.gov/niosh/leadpg.html
OSHA http://www.osha-slc.gov/SLTC/lead/index.html