Review Article

Lead Exposure: A Summary of Global Studies and the Need for New Studies from Saudi Arabia

A. P. Shaik,1 S. A. Sultana,1 and A. H. Alsaeed1,2

1 College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia
2 Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

Correspondence should be addressed to A. H. Alsaeed; abbasalsaeed@yahoo.com

Received 27 May 2014; Accepted 16 July 2014; Published 19 August 2014

Academic Editor: Marco E. M. Peluso

Copyright © 2014 A. P. Shaik et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Lead poisoning (plumbism) can cause irreversible genetic and reproductive toxicity, hematological effects, neurological damage, and cardiovascular effects. Despite many efforts to minimize lead poisoning, it continues to be a major health concern in many developing and developed countries. Despite efforts to control lead exposure and toxicity, serious cases of lead poisoning increasingly occur as a result of higher vehicular traffic and industrialization. The biomarkers for identification of genetic susceptibility to a particular disease are useful to identify individuals who are at risk for lead poisoning. Although many such studies have been taken up elsewhere, very few studies were performed in Saudi Arabia to assess susceptibility to lead poisoning. This indicates an urgent need for testing of susceptible individuals. The present paper was planned to understand the genetic susceptibility to lead toxicity in the various population studies conducted worldwide and also to correlate it with the current scenario in Saudi Arabia. Such studies are necessary for appropriate precautions in terms of diet and avoiding exposure to be used in order to prevent adverse health effects.

1. Introduction

Genetic biomonitoring of populations exposed to hazardous substances like heavy metals could create an early warning system for genetic diseases [1, 2]. Many types of occupational exposure pose serious health hazards [3]. Lead is a ubiquitous metal that has been used in more than 900 occupations, including battery manufacturing, smelting, and mining [4]. Lead poisoning occurs as a result of ingestion or inhalation of inorganic lead particles or through transdermal absorption of organic alkyl lead [2, 5]. Once absorbed, most of the lead binds to erythrocytes causing most of the toxic effects [6, 7]. Bone lead accounts for more than 95% of the lead burden in adults and 70% of the burden in children [8, 9]. Lead exposure in the general population (including children) occurs primarily through ingestion; however, inhalation also contributes to lead body burden and may be the major contributor for workers in lead-related occupations [10]. Once absorbed, lead may be stored for long periods in mineralizing tissue (i.e., teeth and bones) and then released again into the bloodstream, especially in times of calcium stress (e.g., pregnancy, lactation, and osteoporosis) or calcium deficiency [11].

Saudi Arabia faces many environmental challenges that can impact negatively human health and productivity [12]. The Kingdom of Saudi Arabia is therefore making concerted efforts to monitor and reduce health hazards [13]. Human populations in this region are increasingly becoming affected by heavy metal lead either occupationally (workers in battery manufacturing units, cement manufacturing companies, battery recycling units, and paint manufacturing companies) or nonoccupationally (families living in and near factories and neighbourhood habitations in addition to indirect use of lead in various home remedies such as kohl and bakhoor) [2, 14]. Although leaded gasoline which was once thought to be a major source of lead exposure across different countries has almost been phased out in Saudi Arabia, the multiple other sources as described above can also significantly impact human health.

Unlike overt lead toxicity, where there is usually one identifiable source, low-level environmental exposure to lead is associated with multiple sources including occupational,
environmental, and home use [9]. Evaluation of the relative contributions of the different sources is therefore complex and likely to differ between areas and population groups [8]. Classically, lead toxicity has been detected using phenotypic estimations of blood lead level; this is now largely being also supported by genotype analyses of ALAD gene polymorphisms which are known to influence the levels of blood lead and thus directly affect the susceptibility of individuals to lead poisoning. Many such studies have been conducted in different populations. However, the literature and work in this area are very minimal in Saudi Arabia and from the Middle Eastern region further preventing the overall understanding of susceptibility to lead poisoning in this region. Therefore, a systematic review of the literature with focus on genotype frequency analyses conducted in different populations was performed using PubMed (January 1990 to December 2013) to understand where the Kingdom stands in terms of these studies vis-à-vis the published literature. Retrieved articles and their bibliographies were evaluated and reviewed independently by 2 medical experts before the shortlisted studies were further analyzed. Brief descriptions of the clinical implications of lead exposure have also been presented.

### 2. Evaluation of Health Risks and the Pathophysiology of Lead Toxicity

Exposure to lead can have a range of biological effects depending on level and duration of exposure; the developing fetus and infants are more sensitive than adults [15, 16]. Impaired hemoglobin synthesis; kidney dysfunction, gastrointestinal disturbances, and bone and joint defects; and acute or chronic damage to the nervous system are the most reported effects [9, 17]. Reportedly, even intermediate concentrations of lead can have subtle, subclinical effects, particularly on neuropsychological developments in children [6, 9]. In addition to causing a disruption of enzymatic process through interaction with electron-donor groups (-sulfhydryl) [9], lead interferes with the sodium-potassium-adenosine triphosphate (Na+/K+ -ATP) pump and increases cellular fragility [10, 15]. Lead interferes with the biosynthesis of heme at several enzymatic steps; the inhibition of δ-aminolevulinic acid dehydratase (ALAD) and heme synthetase enzyme which requires eight zinc ions as cofactors for full activity [31]. 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 producing an enzyme which modifies the kinetics of lead upon exposure. ALAD 2-2 and 1-2 heterozygotes produce an enzyme that is more electrongative than that of ALAD-1 homozygotes and thus individuals with these genotypes have increased blood lead levels and lower concentrations of aminolevulinic acid in plasma, lower zinc protoporphyrin levels, lower cortical bone lead concentrations, higher concentrations of trabecular (spongy) bone lead, and lower amounts of DMSA chelatable lead compared to ALAD 1-1 individuals.

### 3. Genetic Susceptibility to Lead Poisoning: ALAD Genotypes

The most commonly studied polymorphism in the ALAD gene, namely, the ALADG177C, yields two codominant alleles, ALAD-1 and ALAD-2. The frequencies of ALAD 1-1, ALAD 1-2, and ALAD 2-2 genotypes vary by geography and race [30]. The ALAD gene is located on chromosome 9q34 encodes the ALAD enzyme (E.C. 4.2.1.24), also known as porphobilinogen synthase composed of eight identical subunits which requires eight zinc ions as cofactors for full activity [31]. 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 producing an enzyme which modifies the kinetics of lead upon exposure. ALAD 2-2 and 1-2 heterozygotes produce an enzyme that is more electronegative than that of ALAD-1 homozygotes and thus individuals with these genotypes have increased blood lead levels and lower concentrations of aminolevulinic acid in plasma, lower zinc protoporphyrin levels, lower cortical bone lead concentrations, higher concentrations of trabecular (spongy) bone lead, and lower amounts of DMSA chelatable lead compared to ALAD 1-1 individuals.

### 4. Global Scenario of ALAD Gene Polymorphism Studies

Determining polymorphisms that affect susceptibility to lead poisoning thus allows identification of susceptible groups thus playing an important role in prevention of occupational and nonoccupational health hazards [32]. A number of studies have assessed the role of ALAD gene polymorphisms in lead toxicity globally (Figures 1 and 2) [26, 28, 33–78]. A total of 24 studies conducted in various countries on subjects with occupational exposure to lead have assessed susceptibility

| Exposure source | Description/exposure pathway | Ref. # |
|-----------------|-----------------------------|--------|
| Bint dahab      | A yellow lead oxide used as a home remedy. | McNiel and Reinhard 1967 [80] |
| Santrinj        | 98% lead oxide used as a home remedy for “gum boils” and “teething.” | McNiel and Reinhard 1967 [80] |
| Traditional Saudi medicine | Orange powder for teething and for antidiarrheal effect. | Abu Melha et al. 1987 [81] |
| Kohl            | 83% lead, believed to strengthen and protect the eyes. | Al-Saleh et al. 1999 [23] |
to lead toxicity with relation to ALAD gene polymorphisms (Figure 2). Around 26 studies estimated ALAD gene polymorphisms in adults who belonged to general population and who were exposed to environmental lead by virtue of close proximity to lead polluted regions or working in factories but without directly using lead (i.e., administrative roles) (Figure 2). In addition, seven general population and environmental studies estimated ALAD gene polymorphisms in children (Figure 3). The mean blood lead levels in most of the studies conducted on occupational exposure were from 10 to 61 μg/dL. Most of the studies conducted in the general population and in adults and children with environmental exposure showed blood lead levels <10 μg/dL. These studies were predominantly conducted in the Caucasian and Asian populations. Although ALAD 1-2 and 2-2 genotypes were present in lesser numbers, it was evident that subjects with ALAD2 allele showed higher blood lead levels compared to ALAD1 allele. ALAD allele was a significant determinant

### Table 2: Studies that estimated lead levels in Saudi Arabia.

| References                  | Lead levels | Percentage of subjects                      |
|-----------------------------|-------------|--------------------------------------------|
| Al-Saleh 1995 [24]          | 5–10 g/dL   | 23.3                                       |
| Al-Saleh et al. 1995 [25]   | 10–20 µg/dL | 15.7                                       |
| Younes et al. 1995 [21]     | 0.318–2.5 µg/dL | 81% of nursing mothers from environmental lead exposure |
| Al-Saleh et al. 1999 [23]   | >20 µg/dL   | 11.4                                       |

![Figure 1: Occupational studies assessing ALAD gene polymorphisms in adults.](image1)

![Figure 2: General population and environmental studies assessing ALAD gene polymorphisms in adults.](image2)
for blood lead concentrations and it is therefore important to characterize subjects based on their genotype since such information will help in keeping appropriate preventive measures in place especially for subjects who have increased susceptibility to lead poisoning [77].

5. Nonoccupational Use of Lead in Home Remedies and Beauty Products in Saudi Arabia

The Lead Newsletter 2 [14] published in 2008 clearly indicates the use of lead containing folk home remedies such as al-murrah in the treatment of colic, stomach aches, and diarrhea; anzroot for gastroenteritis; bint al dahab; bint; bent dahab for diarrhea, colic, constipation, and general neonatal use; bokhoor to calm infants; cebagin; farouk for teething powder; henna for hair; kohl and surma as cosmetic, astringent for eye injuries, umbilical stump, and teething powder; and satrinj as teething powder (Table 2).

6. Studies from Saudi Arabia

The definition of an elevated concentration of lead in the blood, according to the Centers for Disease Control and Prevention [9], is 10 μg/dL. However, accumulating evidence indicates that some health effects can occur below this threshold. The data from Table 2 shows percentages of lead levels in children and in adults in Saudi Arabia, estimated up to 1999; there are few studies such as these in Saudi Arabia in adults and in adolescents after 1999. One recent study published in 2012 conducted in children from Madinah region [79] showed mean BLL of 5 μg/dL. Breast milk samples from mothers residing near industrial areas showed higher lead levels than from subjects living in areas with no environmental exposure [21]. The study by Yaish et al. [22] in children from Saudi Arabia indicates that lead poisoning is common and poses a major public health hazard and also reported encephalopathy in children with blood lead levels of 50–60 μg/dL. The very few studies so far in Saudi population limit our understanding of the frequency of ALAD genotypes in this region.

Because lead is a commonly used heavy metal, genetic testing to identify subjects who are predisposed to react adversely to this particular environmental exposure could play a significant role in efforts to reduce the disease burden associated with lead toxicity [8]. The Saudi Arabian population is comprised of a unique genetic makeup and it is therefore important to study the Arab populations to understand the extent of ALAD gene variations and to understand if this population is less or more prone to lead poisoning. Given the heterogeneity of the Arab populations, and the absence of such studies in this region, ALAD genetic polymorphism studies will help in raising awareness to lead toxicity.

Although physicians have a very good understanding of the therapeutic measures that need to be taken in case of toxicity, it is essential for research scientists to work towards bridging the gap between understanding the toxic effects of exposure and their modulations at a cellular and molecular level in order to devise appropriate treatment regimen. Genetic monitoring studies in the Kingdom of Saudi Arabia that employ a holistic approach towards understanding lead toxicity will help physicians to concentrate more on individualistic therapies. Identification of susceptibility through population-based screening methods will definitely improve understanding of the health effects of heavy metal lead in the Saudi Arabian population. This approach will aid in appropriate management of risk factors and mitigating lead poisoning through community-wide awareness programs.

Conflict of Interests

The authors report no conflicting interests with respect to this study.

Acknowledgment

The authors are thankful to the Deanship of Scientific Research, King Saud University, Riyadh, for funding this work through the Research Group Project no. RGP-VPP-259.

References

[1] A. M. Osorio and J. Melius, “Lead poisoning in construction,” Occupational Medicine, vol. 10, no. 2, pp. 353–361, 1995.
[2] RTECS; Lead. Registry of Toxic Effects on Chemical Substances. National Institute of Occupational Safety and Health. MDL Information Systems, Inc, 2007.
[3] D. L. Eaton and C. D. Klaassen, “Principles of toxicology,” in Casarett & Doull’s Toxicology: The Basic Science of Poisons, C. D. Klaassen, Ed., pp. 13–33, McGraw-Hill, New York, NY, USA, 5th edition, 1996.
[4] ChemIDplus, Lead and Lead Compounds, U.S. National Library of Medicine, Bethesda, Md, USA, 2005.
[5] D. C. Bellinger, “Lead,” Pediatrics, vol. 113, no. 4, pp. 1016–1022, 2004.
[6] Agency for Toxic Substances and Disease Registry (ATSDR), “Toxicological Profile for Lead,” U.S. Department of Health and Human Services, 1998.
[7] D. E. B. Fleming, D. R. Chettle, J. G. Wetmur et al., "Effect of the δ-aminolevulinate dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers," Environmental Research, vol. 77, no. 1, pp. 49–61, 1998.

[8] HSDB, “Lead -Hazardous Substances Data Bank,” National Library of Medicine, 2007. http://toxnet.nlm.nih.gov/.

[9] Centers for Disease Control and Prevention (CDC), "Adult blood lead epidemiology and surveillance—United States fourth quarter 1996," Morbidity and Mortality Weekly Report, vol. 46, no. 16, pp. 358–359, 1997.

[10] H. L. Needleman, “Lead poisoning,” Annual Review of Medicine, vol. 55, pp. 209–222, 2004.

[11] ExToxNet, "Extension Toxicology Network Cornell University," 2000. http://pme.cce.cornell.edu/profiles/extoxnet/.

[12] http://www.pme.gov.sa/en/en/airpollution.asp.

[13] http://www.un.org/esa/sustdev/csd/csd15/statements/saudiarabia_28feb_air.pdf.

[14] Lead Newsletter 2, http://wwwmedicine.virginia.edu/clinical/departments/emergency-medicine/fellowships/medtox/education/lead-newsletters-lead-lead-newslett-vol-4-issue-1.pdf.

[15] R. J. Šrám and B. Binková, “Molecular epidemiology studies on occupational and environmental exposure to mutagens and carcinogens, 1997–1999,” Environmental Health Perspectives, vol. 108, supplement 1, pp. 57–70, 2000.

[16] R. A. Goyer, “Lead,” in Patty's Toxicology, E. Bingham, B. Cohrssen, and C. H. Powell, Eds., 675, p. 611, John Wiley & Sons, New York, NY, USA, 5th edition, 2001.

[17] L. M. Fels, M. Wünsch, J. Baranowski et al., "Adverse effects of chronic low level lead exposure on kidney function—a risk group study in children," Nephrology Dialysis Transplantation, vol. 13, no. 9, pp. 2248–2256, 1998.

[18] B. K. May, S. C. Dogra, T. J. Sadlon, C. R. Bhasker, T. C. Cox, and S. S. Bottomley, "Molecular regulation of heme biosynthesis in higher vertebrates," Progress in Nucleic Acid Research and Molecular Biology, vol. 51, pp. 1–51, 1995.

[19] P. Froome, E. Kristal-Boneh, J. Benbassat, R. Ashkanazi, and J. Ribak, "Lead exposure in battery-factory workers is not associated with anemia," Journal of Occupational & Environmental Medicine, vol. 41, no. 2, pp. 120–123, 1999.

[20] M. Ahamed, S. Verma, A. Kumar, and M. K. J. Siddiqui, "Environmental exposure to lead and its correlation with biochemical indices in children," Science of the Total Environment, vol. 346, no. 1–3, pp. 48–55, 2005.

[21] B. Younes, A. A. Al-Meshari, A. Al-Hakeem et al., “Lead concentration in breast milk of nursing mothers living in Riyadh,” Annals of Saudi Medicine, vol. 15, no. 3, pp. 249–251, 1995.

[22] H. M. Yaish, G. A. Niazi, and A. Al Sobhy, "Lead poisoning among Saudi children," Annals of Saudi Medicine, vol. 13, no. 5, pp. 395–401, 1993.

[23] I. Al-Saleh, M. Nester, E. Devol, N. Shinwari, and S. Al-Shahria, “Determinants of blood lead levels in Saudi Arabian schoolgirls,” International Journal of Occupational and Environmental Health, vol. 5, no. 2, pp. 107–114, 1999.

[24] I. A. Al-Saleh, “Lead exposure in Saudi Arabia and its relationship to smoking,” BioMetals, vol. 8, no. 3, pp. 243–245, 1995.

[25] I. Al-Saleh, M. A. Khalil, and A. Taylor, "Lead, erythrocyte protoporphyrin, and hematological parameters in normal maternal and umbilical cord blood from subjects of the Riyadh region, Saudi Arabia," Archives of Environmental Health, vol. 50, no. 1, pp. 66–73, 1995.

[26] J. G. Wetmur, G. Lehnert, and R. J. Desnick, “The δ-aminolevulinate dehydratase polymorphism: higher blood lead levels in lead workers and environmentally exposed children with the 1-2 and 2-2 isoforms,” Environmental Research, vol. 56, no. 2, pp. 109–119, 1991.

[27] J. G. Wetmur, A. H. Kaya, M. Plewinska, and R. J. Desnick, "Molecular characterization of the human δ-aminolevulinate dehydratase 2 (ALAD2) allele: implications for molecular screening of individuals for genetic susceptibility to lead poisoning," The American Journal of Human Genetics, vol. 49, no. 4, pp. 757–763, 1991.

[28] B. S. Schwartz, B.-K. Lee, W. Stewart, K.-D. Ahn, K. Springer, and K. Kelsey, "Associations of δ-aminolevulinic acid dehydratase genotype with plant, exposure duration, and blood lead and zinc protoporphyrin levels in Korean lead workers," American Journal of Epidemiology, vol. 142, no. 7, pp. 738–745, 1995.

[29] ATSDR (Agency for Toxic Substances and Disease Registry), Interaction Profile for Chlorpyrifos, Lead, Mercury, and Methylmercury, ATSDR (Agency for Toxic Substances and Disease Registry), Atlanta, GA, USA, 2006.

[30] A. O. Onalaja and L. Claudio, "Genetic susceptibility to lead poisoning," Environmental Health Perspectives, vol. 108, supplement 1, pp. 23–28, 2000.

[31] S. N. Kelada, E. Shelton, R. B. Kaufmann, and M. J. Houyry, "δ-aminolevulinic acid dehydratase genotype and lead toxicity: A HuGE review," The American Journal of Epidemiology, vol. 154, no. 1, pp. 1–13, 2001.

[32] A. P. Shaik and K. Jamil, "Lead exposure: assessment of genotoxicity and gene polymorphisms in the study group," Journal of Hazardous Materials, vol. 168, pp. 918–924, 2009.

[33] J. García-Lestón, J. Roma-Torres, M. Vilares et al., "Genotoxic effects of occupational exposure to lead and influence of polymorphisms in genes involved in lead toxicokinetics and in DNA repair," Environment International, vol. 43, no. 1, pp. 29–36, 2012.

[34] I. A. Bergdahl, L. Gerhardsson, A. Schütz, R. J. Desnick, J. G. Wetmur, and S. Skerfving, "Delta-aminolevulinic acid dehydratase polymorphism: Influence on lead levels and kidney function in humans," Archives of Environmental Health, vol. 52, no. 2, pp. 91–96, 1997.

[35] B. H. Alexander, H. Checkoway, P. Costa-Mallen et al., "Interaction of blood lead and δ-aminolevulinic acid dehydratase genotype on markers of heme synthesis and sperm production in lead smelter workers," Environmental Health Perspectives, vol. 106, no. 4, pp. 213–216, 1998.

[36] A. Leroyer, B. Leleu, B. Dehon, P. Frimat, F. Broly, and C. Nisse, “Influence of delta-aminolevulinic Acid dehydratase gene polymorphism on selected lead exposure biomarkers in a cohort of ex-smelter workers,” Journal of Toxicology and Environmental Health A, vol. 76, no. 15, pp. 895–906, 2013.

[37] K. Nomiyama, H. Nomiyama, and K. Xin, "Erythrocyte δ-aminolevulinic acid dehydratase genotype and other mechanisms affecting workers' susceptibility to lead," Journal of Occupational and Environmental Medicine, vol. 41, no. 8, pp. 662–668, 1999.

[38] T. Sakai, "Biomarkers of lead exposure," Industrial Health, vol. 38, no. 2, pp. 127–142, 2000.

[39] X. Ye, C. Wu, H. Fu, S. Yang, Y. Lu, and W. Ni, "Associations of blood lead levels, kidney function, and blood pressure with δ-aminolevulinic acid dehydratase and vitamin D receptor gene..."
polymorphisms,” *Toxicology Mechanisms and Methods*, vol. 13, no. 2, pp. 139–146, 2003.

[40] H. Kim, S. Lee, G. Lee, Y. Hwangbo, K. Ahn, and B. Lee, “The protective effect of δ-aminolevulinic acid dehydratase 1 and 2-2 isozymes against blood lead with higher hematologic parameters,” *Environmental Health Perspectives*, vol. 112, no. 5, pp. 538–541, 2004.

[41] F. Wu, P. Chang, C. Wu, J. Lai, and H. Kuo, “Lack of association of δ-aminolevulinic acid dehydratase genotype with cytogenetic damage in lead workers,” *International Archives of Occupational and Environmental Health*, vol. 77, no. 6, pp. 395–400, 2004.

[42] S. Chia, E. Yap, and K. Chia, “δ-aminolevulinic acid dehydratase (ALAD) polymorphism and susceptibility of workers exposed to inorganic lead and its effects on neurobehavioral functions,” *NeuroToxicology*, vol. 25, no. 6, pp. 1041–1047, 2004.

[43] K. Theppaeng, B. Schwartz, B. Lee et al., “Associations of patella lead with polymorphisms in the vitamin D receptor, δ-aminolevulinate acid dehydratase and endothelial nitric oxide synthase genes,” *Journal of Occupational and Environmental Medicine*, vol. 46, no. 6, pp. 528–537, 2004.

[44] S. E. Chia, H. Zhou, M. T. Tham et al., “Possible influence of δ-aminolevulinic acid dehydratase polymorphism and susceptibility to renal toxicity of lead: a study of a Taiwanese population,” *Environmental Health Perspectives*, vol. 113, no. 10, pp. 1313–1317, 2005.

[45] V. M. Weaver, B. S. Schwartz, B. G. Jaar et al., “Associations of uric acid with polymorphisms in the δ-aminolevulinic acid dehydratase, vitamin D receptor, and nitric oxide synthase genes in Korean lead workers,” *Environmental Health Perspectives*, vol. 113, no. 11, pp. 1509–1515, 2005.

[46] S. Chia, H. J. Zhou, E. Yap et al., “Association of renal function and δ-aminolevulinic acid dehydratase polymorphism among Vietnamese and Singapore workers exposed to inorganic lead,” *Occupational and Environmental Medicine*, vol. 63, no. 3, pp. 180–186, 2006.

[47] A. P. Shaik and K. Jamil, “A study on the molecular analysis of ALAD gene polymorphisms,” *Toxicology and Industrial Health*, vol. 24, no. 7, pp. 501–506, 2008.

[48] W. Wananukul, T. Sura, and P. Salaitanawatwong, “Polymorphism of delta-aminolevulinic acid dehydratase and its effect on blood lead levels in Thai workers,” *Archives of Environmental and Occupational Health*, vol. 61, no. 2, pp. 67–72, 2006.

[49] A. Gao, X. Lu, Q. Li, and L. Tian, “Effect of the delta-aminolevulinic acid dehydratase gene polymorphism on renal and neurobehavioral function in workers exposed to lead in China,” *Science of the Total Environment*, vol. 408, no. 19, pp. 4052–4055, 2010.

[50] G. Zheng, L. Tian, Y. Liang et al., “δ-Aminolevulinic acid dehydratase genotype predicts toxic effects of lead on workers’ peripheral nervous system,” *NeuroToxicology*, vol. 32, no. 4, pp. 374–382, 2011.

[51] Y. Yang, J. Wu, and P. Sun, “Effects of delta-aminolevulinic acid dehydratase polymorphisms on susceptibility to lead in han subjects from southwestern China,” *International Journal of Environmental Research and Public Health*, vol. 9, no. 7, pp. 2326–2338, 2012.

[52] F. Pérez-Bravo, M. Ruz, M. J. Morán-Jiménez et al., “Association between aminolevulinate dehydrogenase genotypes and blood lead levels in children from a lead-contaminated area in Antofagasta, Chile,” *Archives of Environmental Contamination and Toxicology*, vol. 47, no. 2, pp. 276–280, 2004.

[53] I. A. Mijares, P. López, J. L. Rosado et al., “Delta-aminolevulinic acid dehydratase genotype and its relationship with blood lead and zinc protoporphyrin levels in lead-exposed children living in a smelter community in Northern Mexico,” *Toxicology Mechanisms and Methods*, vol. 16, no. 1, pp. 41–47, 2006.

[54] C. Sobin, M. Gutierrez, and H. Alterio, “Polymorphisms of delta-aminolevulinic acid dehydratase (ALAD) and peptide transporter 2 (PepT2) genes in children with low-level lead exposure,” *NeuroToxicology*, vol. 30, no. 6, pp. 881–887, 2009.

[55] N. Pawlas, K. Broberg, E. Olevińska, A. Prokopowicz, S. Skerfving, and K. Pawlas, “Modification by the genes ALAD and VDR of lead-induced cognitive effects in children,” *NeuroToxicology*, vol. 33, no. 1, pp. 37–43, 2012.

[56] X. Shen, S. Wu, C. Yan et al., “Delta-aminolevulinate dehydratase polymorphism and blood lead levels in Chinese children,” *Environmental Research*, vol. 85, no. 3, pp. 185–190, 2001.

[57] Y. Chen, J. Zhao, J. Liu, J. Cui, L. Li, and W. Tian, “Lack of association of δ-aminolevulinic acid dehydratase genotype with blood lead levels in environmentally exposed children of Uygur and Han populations,” *Acta Paediatrica*, vol. 97, no. 12, pp. 1717–1720, 2008.

[58] F. Kamel, D. M. umbach, T. A. Lehman et al., “Amyotrophic lateral sclerosis, lead, and genetic susceptibility: Polymorphisms in the δ-aminolevulinic acid dehydratase and vitamin D receptor genes,” *Environmental Health Perspectives*, vol. 113, no. 10, pp. 1335–1339, 2003.

[59] E. B. Southard, A. Roff, T. Fortugno et al., “Lead, calcium uptake, and related genetic variants in association with renal cell carcinoma risk in a cohort of male finnish smokers,” *Cancer Epidemiology Biomarkers and Prevention*, vol. 21, no. 1, pp. 191–201, 2012.

[60] M. F. Montenegro, F. Barbosa Jr., V. C. Sandrim, R. F. Gerlach, and J. E. Tănus-Santos, “Ethnicity affects the distribution of δ-aminolevulinic acid dehydratase (ALAD) genetic variants,” *Clinica Chimica Acta*, vol. 367, no. 1-2, pp. 192–195, 2006.

[61] J. Weuve, K. T. Kelsey, I. Schwartz et al., “Delta-aminolevulinic acid dehydratase polymorphism and the relation between low level lead exposure and the Mini-Mental Status Examination in older men: the Normative Aging Study,” *Occupational and Environmental Medicine*, vol. 63, no. 11, pp. 746–753, 2006.

[62] J. Weuve, K. T. Kelsey, I. Schwartz et al., “Delta-aminolevulinic acid dehydratase polymorphism and the relation between low level lead exposure and the mini-mental status examination in older men: the Normative Aging Study,” *Occupational and Environmental Medicine*, vol. 63, no. 11, pp. 746–753, 2007, Erratum in: Occupational and Environmental Medicine, vol. 64, no. 4, pp. 288, 2007.

[63] P. Rajan, K. T. Kelsey, I. D. Schwartz et al., “Lead burden and psychiatric symptoms and the modifying influence of the δ-aminolevulinic acid dehydratase (ALAD) polymorphism: the VA Normative Aging Study,” *American Journal of Epidemiology*, vol. 166, no. 12, pp. 1400–1408, 2007.

[64] E. F. Krieg Jr., M. A. Butler, M. Chang et al., “Lead and cognitive function in ALAD genotypes in the third National Health and Nutrition Examination Survey,” *Neurotoxicology and Teratology*, vol. 31, no. 6, pp. 364–371, 2009.

[65] E. D. Louis, L. Applegate, J. H. Graziano, M. Parides, V. Slavkovich, and H. K. Bhat, “Interaction between blood lead concentration and δ-amino-levulinic acid dehydratase gene polymorphisms increases the odds of essential tremor,” *Movement Disorders*, vol. 20, no. 9, pp. 1170–1177, 2005.
[66] C. Mark Smith, X. Wang, H. Hu, and K. T. Kelsey, "A polymorphism in the δ-aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead," *Environmental Health Perspectives*, vol. 103, no. 3, pp. 248–253, 1995.

[67] H. Hu, M. T. Wu, Y. Cheng, D. Sparrow, S. Weiss, and K. Kelsey, "The δ-aminolevulinic acid dehydratase (ALAD) polymorphism and bone and blood lead levels in community-exposed men: the normative aging study," *Environmental Health Perspectives*, vol. 109, no. 8, pp. 827–832, 2001.

[68] F. Fang, L. C. Kwee, K. D. Allen et al., "Association between blood lead and the risk of amyotrophic lateral sclerosis," *The American Journal of Epidemiology*, vol. 171, no. 10, pp. 1126–1133, 2010.

[69] F. Scinicariello, A. Yesupriya, M. Chang, and B. A. Fowler, "Modification by ALAD of the association between blood lead and blood pressure in the U.S. population: results from the Third National Health and Nutrition Examination Survey," *Environmental Health Perspectives*, vol. 118, no. 2, pp. 259–264, 2010.

[70] J. Fujihara, T. Agusa, T. Yasuda et al., "Ethnic variation in genotype frequencies of δ-aminolevulinic acid dehydratase (ALAD)," *Toxicology Letters*, vol. 191, no. 2-3, pp. 236–239, 2009.

[71] A. O. Moreira, A. Almeida, A. Costa et al., "Genotyping an ALAD polymorphism with real-time PCR in two populations from the Iberian peninsula," *Biochemical Genetics*, vol. 50, no. 7-8, pp. 560–564, 2012.

[72] L. Hsieh, S. Liou, Y. Chen, L. Tsai, T. Yang, and T. Wu, "Association between aminolevulinate dehydrogenase genotype and blood lead levels in Taiwan," *Journal of Occupational and Environmental Medicine*, vol. 42, no. 2, pp. 151–155, 2000.

[73] M. Wu, K. Kelsey, J. Schwartz, D. Sparrow, S. Weiss, and H. Hu, "A δ-aminolevulinic acid dehydratase (ALAD) polymorphism may modify the relationship of low-level lead exposure to uricemia and renal function: the normative aging study," *Environmental Health Perspectives*, vol. 111, no. 3, pp. 335–340, 2003.

[74] Y. Zheng, W. Song, and Y. Wang, "The gene polymorphism of delta-aminolevulinic acid dehydratase (ALAD) in 530 cases of Chinese Han population," *Zhonghua Yu Fang Yi Xue Za Zhi*, vol. 35, no. 1, pp. 16–18, 2001.

[75] K. Miyaki, H. Lwin, K. Masaki et al., "Association between a polymorphism of aminolevulinate dehydrogenase (ALAD) gene and blood lead levels in Japanese subjects," *International Journal of Environmental Research and Public Health*, vol. 6, no. 3, pp. 999–1009, 2009.

[76] Y. Duydu and H. S. Süzên, "Influence of δ-aminolevulinic acid dehydratase (ALAD) polymorphism on the frequency of sister chromatid exchange (SCE) and the number of high-frequency cells (HFCs) in lymphocytes from lead-exposed workers," *Mutation Research*, vol. 540, no. 1, pp. 79–88, 2003.

[77] M. A. Zolaly, M. I. Hanafi, N. Shawky, K. el-Harbi, and A. M. Mohamadin, "Association between blood lead levels and environmental exposure among Saudi schoolchildren in certain districts of Al-Madinah," *International Journal of General Medicine*, vol. 5, pp. 355–364, 2012.

[80] J. R. McNiel and M. C. Reinhard, "Lead poisoning from home remedies," *Clinical Pediatrics*, vol. 6, no. 3, pp. 150–156, 1967.

[81] A. Abu Melha, N. A. Ahmed, and A. Y. El Hassan, "Traditional remedies and lead intoxication," *Tropical and Geographical Medicine*, vol. 39, no. 1, pp. 100–103, 1987.