A cross-sectional study was performed to evaluate the influence of polymorphisms in the δ-aminolevulinic acid dehydratase (ALAD) and vitamin D receptor (VDR) genes on blood lead, tibia lead, and dimercaptosuccinic acid (DMSA)-chelatable lead levels in 798 lead workers and 135 controls without occupational lead exposure in the Republic of Korea. Tibia lead was assessed with a 30-min measurement by 109Cd-induced K-shell X-ray fluorescence, and DMSA-chelatable lead was estimated as 4-hr urinary lead excretion after oral administration of 10 mg/kg DMSA. The primary goals of the analysis were to examine blood lead, tibia lead, and DMSA-chelatable lead levels by ALAD and VDR genotypes, controlling for covariates; and to evaluate whether ALAD and VDR genotype modified relations among the different lead biomarkers. There was a wide range of blood lead (4–86 µg/dL), tibia lead (7–323 µg Pb/g bone mineral), and DMSA-chelatable lead (4.8–2,103 µg) levels among lead workers. Among lead workers, 9.9% (n = 79) were heterozygous for the ALAD2 allele and there were no homozygotes. For VDR, 10.7% (n = 85) had the Bb genotype, and 0.5% (n = 4) had the BB genotype. Although the ALAD and VDR genes are located on different chromosomes, lead workers homozygous for the ALAD1 allele were much less likely to have the VDR Bb genotype (crude odds ratio = 0.29, 95% exact confidence interval = 0.06–0.91). In adjusted analyses, subjects with the ALAD2 allele had higher blood lead levels (on average, 2.9 µg/dL, p = 0.07) but no difference in tibia lead levels compared with subjects without the allele. In adjusted analyses, lead workers with the VDR B allele had significantly (p < 0.05) higher blood lead levels (on average, 4.2 µg/dL), chelatable lead levels (on average, 37.3 µg), and tibia lead levels (on average, 6.4 µg/g) than did workers with the VDR BB genotype. The current data confirm past observations that the ALAD gene modifies the toxicokinetics of lead and also provides new evidence that the VDR gene does so as well. Key words: δ-aminolevulinic acid dehydratase, bone lead, cross-sectional study, lead, polymorphisms, vitamin D receptor, X-ray fluorescence.
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**Study population.** Participation in the study was voluntary, and all participants provided written, informed consent. Subjects were paid approximately $30 for their participation. Lead workers were recruited from 24 different lead-using facilities, with participation in most facilities exceeding 80% (16). Retired workers from three facilities who had received medical surveillance services by Soonchunhyang University for several years were also recruited to participate in the study. Routine, government-mandated industrial hygiene sampling revealed that the study plants did not have significant amounts of other heavy metals such as cadmium. Controls without occupational lead exposure were recruited from an air conditioner assembly plant that did not use lead or other heavy metals. The following data were collected or measured on all study subjects: a standardized interview for demographic, medical history, and occupational history; a neurobehavioral test battery consisting of examiner-administered tests; blood pressure, peripheral vibration threshold and pinch and grip strength; a 10-mL blood sample; a 4-hour urine sample after oral administration of 10 mg/kg DM SA to measure DM SA-chelatable lead (25). Urine lead levels were measured in the laboratories of the Wadsworth Center at the New York State Department of Health, Albany, New York. Urinary lead concentrations were determined by electrothermal atomization atomic absorption spectrometry (Perkin-Elmer Model 4100ZL, Norwalk, CT) using previously published methods (26). Urinary lead excretion was highly correlated with lead excretion adjusted for differences, generally small, in urine collection times (Pearson's \( r = 0.98 \)), so only the unadjusted data are presented.

**ALAD and VDR genotyping.** We completed ALAD and VDR genotyping on 798 and 795 subjects, respectively. VDR genotyping was completed using previously published methods (13). In brief, genomic DNA was extracted from whole blood by using the QIAtamp Blood Kit (QIAGEN, Hilden, Germany), and the BsmI polymorphic site in intron 8 was amplified by polymerase chain reaction (PCR) using the primers originating in exon 7 (primer 1: 5'-CACCAAGAC-TACAATC-CCGTCAGTGA-3') and intron 8 (primer 2: 5'-AACCCAGCAGGA-GAGGTCAGGG-3'). Subjects homozygous for the presence of the BsmI restriction site are designated BB, heterozygotes are designated Bb, and those homozygous for the absence of the site are designated BB.

A modified PCR-based protocol was used for ALAD genotyping and has been previously described (3–5). In brief, the initial amplification, using 3' and 5' oligonucleotide primers (5'-AGACAGACATTAGTCCTAGTA-3') and (5'-GGCAGAACCAAGCG-TCCATT-3'), generates a 916 base pair fragment. A second round of amplification uses a pair of nested primers (provided by J. W. Wientrh, sequences (5'-CAGAGCTTTCACACGTTGGA-3') and (5'-CAGACATGTTGGAGTGA3'), respectively, and generates an 887 base pair fragment. The amplified fragment was cleaved at the diagnostic MspI site, only present in the ALAD2 allele, and three isoforms are observed, designated ALAD1-1, ALAD1-2, and ALAD2-2.

**Statistical analysis.** The primary goals of the analysis were to examine blood lead, tibia lead, and DMSA-chelatable lead levels by ALAD and VDR genotypes, controlling for covariates; and to evaluate whether ALAD and VDR genotype modified relations among the different lead biomarkers. Articles between ALAD and VDR genotype were evaluated in contingency tables using odds ratios (ORs) and 95% exact confidence intervals (CIs) calculated with Epi Info version 6.04b (Centers for Disease Control and Prevention, Atlanta, GA).

We used linear regression to separately model blood lead, tibia lead, and DMSA-chelatable lead levels, controlling for confounding variables, using statistical software programs of SAS Institute, Inc. (Cary, NC). In these regression models, only lead workers, not controls, were included. Covariates examined in linear regression models included age, sex, creatinine clearance (4-hr), hemoglobin, hematocrit, weight, height, body mass index, job duration, and tobacco and alcohol consumption (never, previous, and current use for each). Covariates were retained in the final regression models if they were either a significant predictor of blood lead, tibia lead, or DMSA-chelatable lead levels, or if they were a confounder of the relations between predictor variables and the lead biomarkers. The decisions regarding the variables in the final regression models were also made to be consistent with prior analyses of the data on the subjects presented here (23). Blood lead was modeled with and without adjustment for hematocrit; as this adjustment did not influence regression results, only unadjusted model results are presented. DMSA-chelatable lead and tibia lead were log-transformed before regressing on covariates because of departures from normality. To estimate the mean adjusted differences between genotypes in the original scale of each lead measure, we exponentiated the predicted value from the regression, separately for each genotype, at the mean value of all continuous covariates and the reference value of all dichotomous covariates. To evaluate nonlinear relations, quadratic terms for continuous variables (i.e., age, job duration, weight, height) were evaluated. We evaluated effect modification by genotype by including cross-product terms between the genetic variables and relevant predictor variables (i.e., age, sex, tibia lead, creatinine clearance).

**Results.**

Demographics and dose measures. Compared to controls without occupational lead exposure, lead-exposed subjects were older (40.5 vs. 34.5 years), had lower education levels (49.9% vs. 19.2% did not complete high school), and a lower proportion were male (79.4% vs. 91.9%; Table 1). The majority of both nonexposed and exposed subjects were current users of tobacco and alcohol products. There was a wide range of blood lead (4–86 µg/dL), tibia lead (7–338 µg/g), and DMSA-chelatable lead (4.8–2,103 µg) levels among lead workers (Table 1). The
corresponding values among nonexposed control subjects were low. Among lead workers, tibia lead was moderately correlated with blood lead (Pearson’s $r = 0.42$), DMSA-chelatable lead ($r = 0.43$), and job duration ($r = 0.40$) (all p-values < 0.01). The correlations of blood lead ($r = 0.13$) and DMSA-chelatable lead ($r = 0.17$) with job duration were much lower than were the correlations of these variables with tibia lead. Blood lead was highly correlated with DMSA-chelatable lead ($r = 0.82$).

Prevalence and associations of genotypes. Among lead workers, 9.9% ($n = 97$) were heterozygous for the ALAD$^2$ allele, and there were no ALAD$^2$ homozygotes; 11.2% ($n = 89$) had at least one copy of the VDR B allele, and 0.5% ($n = 4$) had the BB genotype. The corresponding values for controls were 8.1% ($n = 11$) for the ALAD$^2$ allele and 8.9% ($n = 12$) and 0.7% ($n = 1$) for one and two copies of the VDR B allele, respectively. Because of the small number of subjects with the BB genotype, all subsequent analysis combined homozygous and heterozygous variant allele carriers.

In unadjusted (crude) analyses, there were no differences in age, job duration, hemoglobin, blood lead, tibia lead, or DMSA-chelatable lead by ALAD genotype (Table 1). In contrast, blood workers with the BB genotype had blood lead levels 4.2 µg/dL higher than subjects with bb, and lead workers with the ALAD$^2$ allele had blood lead levels 3.6 µg/dL higher than subjects without the allele. There was no evidence of gene–gene interaction in these models (evaluated by controlling for the two genotypes, lead workers with the VDR B polymorphism had blood lead levels 4.2 µg/dL higher than subjects with bb, and lead workers with the ALAD$^2$ allele had blood lead levels 3.6 µg/dL higher than subjects without the allele. There was no evidence of gene–gene interaction in these models (evaluated by

### Table 1. Description of study subjects, October 1997 to August 1999, Republic of Korea.

| Characteristic | Lead-exposed subjects ($n = 798$) | Controls ($n = 135$) |
|---------------|----------------------------------|----------------------|
| Age (years)   | 40.5 ± 10.1 (17.8–64.8)          | 34.5 ± 9.1 (22.0–60.2) |
| Lead work (job duration years) | 8.2 ± 6.5 (0.1–16.2) | NA$^a$ |
| Height (cm)   | 164.7 ± 6.1 (127.8–186.0)        | 167.9 ± 6.2 (148.0–183.4) |
| Weight (kg)   | 62.5 ± 9.1 (37.4–72.7)           | 66.9 ± 9.0 (48.0–93.3) |
| Body mass index (kg/m²) | 23.0 ± 3.0 (15.7–37.4) | 23.7 ± 2.6 (18.5–31.0) |
| Blood lead (µg/dL) | 32.0 ± 15.0 (4–86)  | 5.3 ± 1.6 (2–10) |
| Tibia lead (µg Pb/g bone mineral) | 37.2 ± 40.4 (17–338) | 5.8 ± 0.7 (11–27) |
| DM SA-chelatable lead (µg)$^b$ | 180.0 ± 284.1 (4.8–2103) | NA$^a$ |
| Hemoglobin (g/dL) | 14.2 ± 1.4 (6.5–17.9) | 15.3 ± 1.2 (11.1–18.2) |
| Creatinine clearance, 4-hr (mL/min) | 114.3 ± 33.9 (112–351.6) | NA$^a$ |
| Educational level$^c$ | Lower school ≤ 6 years | 183 (23.0) |
| | Higher school (7–8 years) | 29 (3.6) |
| | Middle school (9–10 years) | 155 (19.4) |
| | High school graduate (11–12 years) | 31 (3.9) |
| | College graduate or more | 27 (3.3) |
| | Missing | 1 (<0.1) |
| Sex, male$^c$ | 634 (79.4) | 124 (91.9) |
| Tobacco use$^c$ | Never | 254 (31.9) |
| | Current use | 455 (57.1) |
| | Past use | 88 (11.0) |
| Alcohol use$^c$ | Never | 231 (29.0) |
| | Current use | 518 (65.0) |
| | Past use | 48 (6.0) |

Values shown are mean ± SD except where indicated.

$^a$The 4-hr urine collection was performed only in subjects who received DMSA.

$^b$DMSA-chelatable lead (µg) was estimated as 4-hr urinary lead excretion after oral administration of 10 mg/kg DM SA, in lead-exposed subjects only (784 subjects completed the urine collection). Values shown are number (%).

| Characteristic | 1-1 | 1-2 | bb | Bb or BB |
|---------------|-----|-----|----|----------|
| Number | 716 | 79 | 709 | 89 |
| Age (years) | 40.5 ± 10.2 | 40.1 ± 9.7 | 40.2 ± 10.0$^a$ | 42.7 ± 10.3$^a$ |
| Job duration (years) | 8.2 ± 6.6 | 8.2 ± 5.8 | 8.4 ± 6.6 | 7.2 ± 5.6 |
| Hemoglobin (g/dL) | 14.2 ± 1.4 | 14.2 ± 1.6 | 14.2 ± 1.4 | 14.1 ± 1.4 |
| Blood lead (µg/dL) | 31.7 ± 14.9 | 34.2 ± 15.9 | 31.6 ± 14.8 | 34.8 ± 16.1 |
| Tuba lead (µg Pb/g bone mineral) | 37.5 ± 40.6 | 31.4 ± 29.5 | 37.1 ± 41.2 | 38.1 ± 33.5 |
| DM SA-chelatable lead (µg)$^b$ | 180.3 ± 181.2 | 161.7 ± 143.0 | 173.5 ± 176.8$^b$ | 217.2 ± 179.7$^b$ |

$^a$ALAD and VDR genotype were completed on 795 and 798 lead workers, respectively. $^b$p < 0.05.

### Table 3. Association of VDR genotype status by ALAD genotype status.

| VDR genotype | ALAD | bb, n (%)$^a$ | Bb or BB, n (%)$^a$ | Total | OR (95% CI)$^b$ |
|--------------|------|---------------|---------------------|-------|-----------------|
| 1-1          | 1-1  | 743 (80.0)    | 96 (10.3)           | 839 (90.3) | 0.46 (0.14–1.15) |
| 1-2          | 1-1  | 85 (9.2)      | 5 (0.5)             | 90 (9.7)  | 8.2 ± 5.6       |
| Total        | 2-1  | 828 (99.1)    | 101 (10.9)          | 929 (100) | 217.2 ± 179.7$^b$ |
| Lead workers | 1-1  | 629 (79.2)    | 86 (10.8)           | 715 (90.1) | 0.29 (0.06–0.91) |
| 1-2          | 1-1  | 76 (9.6)      | 3 (0.4)             | 79 (10.0) | 7.2 ± 5.6       |
| Total        | 1-2  | 705 (88.8)    | 89 (11.2)           | 794 (100) | 0.29 (0.06–0.91) |
| Controls without occupational lead exposure | 1-1  | 114 (84.4)    | 10 (7.4)            | 124 (91.9) | 2.53 (0.23–14.84) |
| 1-2          | 1-1  | 9 (6.7)       | 2 (1.5)             | 11 (8.1)  | 7.2 ± 5.6       |
| Total        | 1-2  | 123 (91.1)    | 12 (8.9)            | 135 (100) | 0.46 (0.14–1.15) |

$^a$Percentage of table totals. $^b$Test for homogeneity of stratum-specific ORs, $p = 0.04$, indicating that the association of the two genotypes in lead workers and controls was different.
inclusion of an ALAD–VDR cross-product term). There was also no evidence of effect modification by ALAD or VDR genotype on the relations of the predictor variables with blood lead levels. The final linear regression model (Table 4) accounted for 35% of the variance in blood lead levels.

Predictors of DMSA-chelatable lead levels in lead-exposed subjects. After adjustment for covariates (age, sex, current tobacco use, body mass index, and 4-hr creatinine clearance), subjects with the VDR B polymorphism had higher DMSA-chelatable lead levels (on average, 32%, or 37.3 µg higher than subjects with VDR bb, \( p < 0.01 \)). In contrast, the ALAD \(^2\) allele was not significantly associated with chelatable lead levels (\( p = 0.69 \)). The relation between creatinine clearance and DMSA-chelatable lead was modified by ALAD genotype (Table 5, model 3). The intercept for lead workers with the ALAD \(^2\) allele was 59% lower than for lead workers with the ALAD \(^1\) allele (\( p = 0.05 \)). Among lead workers with only the ALAD \(^1\) allele, chelatable lead levels increased 5.8 µg for each increase of 10 mL/min in creatinine clearance near its mean value (\( p < 0.01 \)); in contrast, among lead workers with the ALAD \(^2\) allele, chelatable lead levels increased 15.5 µg for each increase of 10 mL/min in creatinine clearance near its mean value (difference in two slopes, \( p = 0.04 \)). The final linear regression models accounted for 25–26% of the variance in DMSA-chelatable lead levels. Addition of blood lead to the models of DMSA-chelatable lead increased the model \( r^2 \) to 79–80%. There were no interactions in these models between blood lead and either of the two genes.

Predictors of tibia lead levels in lead-exposed subjects. After adjustment for age (linear and quadratic terms), sex, job duration, and body mass index, ALAD genotype was not associated with tibia lead levels (Table 6, model 1, \( p = 0.73 \)), but VDR genotype was associated (Table 6, model 2, \( p = 0.03 \)). On average, subjects with the VDR B allele had tibia lead levels that were 29%, or 6.4 µg/g, higher than did subjects without the allele. The influence of the VDR B allele on tibia lead levels was larger than was the influence of the ALAD \(^2\) allele. The mechanism by which these genes influence blood lead levels may differ. ALAD \(^2\) and VDR B were associated with higher blood lead levels, however; only VDR B was associated with higher tibia lead levels (\( p < 0.03 \)). In adjusted analyses, subjects with the VDR B allele had significantly (\( p < 0.05 \)) higher blood lead levels (on average, 4.2 µg/dL).

### Table 4. Linear regression modeling of blood lead, Korean lead workers, 1997–1999.\(^a\)

| Independent variable | Units of \( \beta \) coefficient | \( \beta \) coefficient | \( \beta \) SE | \( p \) Value |
|----------------------|---------------------------------|------------------------|-------------|-------------|
| Age                  | µg/dL/year                      | 0.286                  | 0.049       | < 0.001     |
| Female               | µg/dL                           | -13.782                | 1.382       | < 0.001     |
| Current smoker       | µg/dL                           | 3.406                  | 1.081       | 0.002       |
| Tibia lead           | µg/dL/µg/g                      | 0.131                  | 0.011       | < 0.001     |
| VDR, Bx vs. bb       | µg/dL                           | 4.183                  | 1.376       | 0.002       |
| ALAD, 12 vs. 11       | µg/dL                           | 3.627                  | 1.445       | 0.01        |

\( a \)model \( r^2 = 0.35 \).

### Table 5. Linear regression modeling of DMSA-chelatable lead, Korean lead workers, 1997–1999.

| Independent variable | Units of \( \beta \) coefficient | \( \beta \) coefficient | \( \beta \) SE | \( p \) Value |
|----------------------|---------------------------------|------------------------|-------------|-------------|
| Model 1              |                                 |                        |             |             |
| Age                  | µg/year                         | 0.033                  | 0.004       | < 0.001     |
| Female               | µg/year                         | -0.958                 | 0.105       | < 0.001     |
| Current smoker       | µg/year                         | 0.299                  | 0.080       | < 0.001     |
| Body mass index      | µg/kg/cm\(^2\)                  | 0.010                  | 0.012       | 0.40        |
| Creatinine clearance | µg/µL/min                       | 0.006                  | 0.003       | < 0.001     |
| VDR, Bx vs. bb       | µg/year                         | 0.282                  | 0.103       | 0.006       |
| Model 2              |                                 |                        |             |             |
| Age                  | µg/year                         | 0.034                  | 0.004       | < 0.001     |
| Female               | µg/year                         | -0.946                 | 0.106       | < 0.001     |
| Current smoker       | µg/year                         | 0.310                  | 0.081       | < 0.001     |
| Body mass index      | µg/kg/cm\(^2\)                  | 0.013                  | 0.012       | 0.26        |
| Creatinine clearance | µg/µL/min                       | 0.006                  | 0.001       | < 0.001     |
| ALAD, 12 vs. 11       | µg/year                         | 0.044                  | 0.108       | 0.69        |
| Model 3              |                                 |                        |             |             |
| Age                  | µg/year                         | 0.034                  | 0.004       | < 0.001     |
| Female               | µg/year                         | -0.937                 | 0.106       | < 0.001     |
| Current smoker       | µg/year                         | 0.307                  | 0.081       | < 0.001     |
| Body mass index      | µg/kg/cm\(^2\)                  | 0.012                  | 0.012       | 0.29        |
| Creatinine clearance | µg/µL/min                       | 0.005                  | 0.001       | < 0.001     |
| ALAD \times creatinine clearance AI | µg/µL/min | 0.008 | 0.004 | 0.04 |

\( a \)DMSA-chelatable lead was log-transformed for these regressions because of departure from normality.

### Table 6. Linear regression modeling of tibia lead, Korean lead workers, 1997–1999.\(^a\)

| Independent variable | Units of \( \beta \) coefficient | \( \beta \) coefficient | \( \beta \) SE | \( p \) Value |
|----------------------|---------------------------------|------------------------|-------------|-------------|
| Model 1              |                                 |                        |             |             |
| Age                  | µg/g/year                       | 0.001                  | 0.005       | 0.002       |
| Age\(^2\)            | µg/g/year\(^2\)                | 0.0003                 | 0.0003      | 0.003       |
| Female               | µg/g                            | -0.407                 | 0.104       | < 0.001     |
| J ob duration        | µg/g/year                       | 0.048                  | 0.007       | < 0.001     |
| Body mass index      | µg/kg/cm\(^2\)                 | 0.033                  | 0.013       | 0.01        |
| ALAD (12 vs. 11)     | µg/g                            | 0.042                  | 0.122       | 0.73        |
| Model 2              |                                 |                        |             |             |
| Age                  | µg/g/year                       | 0.013                  | 0.005       | 0.006       |
| Age\(^2\)            | µg/g/year\(^2\)                | 0.0003                 | 0.0003      | 0.002       |
| Female               | µg/g                            | -0.412                 | 0.103       | < 0.001     |
| J ob duration        | µg/g/year                       | 0.050                  | 0.007       | < 0.001     |
| Body mass index      | µg/kg/cm\(^2\)                 | 0.030                  | 0.013       | 0.02        |
| VDR (Bx vs. bb)      | µg/g                            | 0.254                  | 0.117       | 0.03        |

\( a \)Tibia lead was log-transformed for these regressions because of departure from normality. \( \# \)model \( r^2 = 0.15 \).
micrograms per deciliter (µg/dL), chelatable lead levels (on average, 37.3 µg/dL), and tibia lead levels (on average, 6.4 µg/g) than did subjects with the VDr genotype. VDR genotype did not modify relations between such factors as age, sex, and renal function and any of the lead dose measures. In part, these observations may be explained by the greater intestinal absorption of lead, or greater uptake and subsequent release of lead from bone, in individuals with VDr B (13.27–32). Vitamin D, after binding to the VDR receptor, increases intestinal absorption of calcium and lead. The VDR B allele has been associated with lower bone mineral densities and higher tibia lead levels (13.15), but the mechanism underlying these observations is not currently known. Interpretation of the observation that lead workers with the VDR B allele have higher tibia lead levels than do workers without VDr B is complicated by the fact that VDR genotype is likely to influence the content of both calcium and lead in bone and tibia lead concentration as measured by XRF is standardized to bone mineral content. Thus, higher tibia lead concentrations can be due to higher lead content, lower calcium content, or both.

In adjusted analyses, subjects with the ALAD2 allele had higher lead levels (on average, 3.6 µg/dL; µ = 0.01) but no differences in tibia or chelatable lead levels compared to subjects without the allele. Creatinine clearance was an important predictor of chelatable lead levels and ALAD genotype modified the relation between creatinine clearance and chelatable lead. Subjects with the ALAD2 allele had larger increases in chelatable lead levels with increasing creatinine clearance than did subjects without the allele. We previously reported that subjects with ALAD2 had lower DMSA-chelatable lead levels than did lead workers with ALAD1 (6). It is important to note that in the previous study, DMSA was administered at 5 mg/kg, and mean DMSA-chelatable lead levels were approximately half of those in the current study, in which workers were administered 10 mg/kg DMSA. These data are consistent with earlier observations that the ALAD2 allele increases erythropoietic binding of lead (3–12). This increase in intraerythropoietic lead may decrease the relative deposition of lead in critical target organs and thus protect against the toxicity of lead.

An unexpected observation was that ALAD and VDR genotypes were associated. These genes are located on different chromosomes. Lead workers with the ALAD1-1 genotype were much less likely to have the VDBb genotype (OR = 0.29, p < 0.05). Although this observation has to be interpreted with caution because only three lead workers had the ALAD1-2 and VDR Bb genotypes, the exact confidence interval did not include 1.0. The data also suggested that the association between the two genotypes in the controls without occupational lead exposure was different, in that controls with the ALAD1-1 genotype were much more likely to have the VDB b genotype (OR = 2.5), and the stratum-specific ORs were significantly different. This is not a stable estimate, however, due to small cell sizes, and requires confirmation. One study reported that differential selection in the lead industry may occur by ALAD genotype (3), and the current data are further evidence that genetic factors may influence the duration of work in the lead industry.

To date, data would suggest that the ALAD1 allele is more likely to confer health risks associated with lead exposure. For the VDR genotype, data are insufficient to determine whether the polymorphisms are likely to modify health risks due to lead and which allele might predispose the alleles for either ALAD or VDR that confer health risk should become less prevalent with increasing duration of occupational exposure to lead (3); this could occur, for example, if the at-risk alleles are associated with the development of acute symptoms that increase the probability of quitting jobs with lead exposure. We have no information in former lead workers on either symptoms or work duration by ALAD or VDR genotype, and serial blood lead measurements from the start of employment are not available for the majority of lead workers. These limitations weaken the inferences that we can make at this time. However, compared to the controls, it appears that lead workers have higher prevalences of both the ALAD2 and VDR B alleles (10.3% vs. 8.1% and 11.4% vs. 8.9%, respectively). This observation would support the inference that the ALAD2 allele is “protective,” as is the VDR B allele, and that there may be selection by genotype among lead workers, but this speculation requires further study.

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