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Original article

Impact of vitamin D receptor gene polymorphisms on blood lead levels in Thai lead exposed workers

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Background: Although lead poisoning has aroused public concern, its toxicokinetics and mechanism of toxicity are still unclear. Vitamin D regulates calcium homeostasis via vitamin D receptor (VDR) and its polymorphisms cause variability of body calcium and bone density. VDR polymorphisms may correlate with the variability of body burden of lead.

Objective: Determine if vitamin D receptor polymorphisms is associated with blood lead in Thai workers exposed to lead.

Subjects and methods: Four hundred fifteen lead exposure workers were recruited in the study. Blood lead level was determined as a biomarker of lead. Five VDR polymorphisms (FokI, BsmI, Apa, TagI, and Cdx2) were studied.

Results: The allele frequencies of F/f, B/b, A/a, T/t, and A/G for FokI, BsamI, ApaI, TagI and Cdx-2 polymorphisms were 059/0.41, 0.07/0.93, 0.32/0.68, 0.94/0.06 and 0.4/0.6, respectively. Gender, smoking status, lead exposure status, BsmI, and TaqI polymorphisms were associated with blood lead level. The BB genotype of BsmI and the tt genotype of TaqI have significantly lower blood lead levels than other genotypes of their polymorphisms.

Conclusion: The BsmI and TaqI polymorphisms of the vitamin D receptor gene had impact on the blood lead level. This association was similar to their effects on calcium. Lead might share the same toxicokinetics with calcium.

Keywords: ApaI, BsmI, Cdx-2, FokI, lead level, lead poisoning, polymorphism, TaqI, vitamin D receptor

Lead causes acute, sub-acute, or chronic poisoning. All types of these toxicities have aroused public concern. Lead toxicokinetics and mechanism of poisoning have not yet been completely elucidated. Lead, calcium, and zinc are bivalent cations. Lead may share the toxicokinetic processes with the other heavy metals that have physiologic function [1, 2].

Vitamin D and its metabolites enhance intestinal absorption and renal reabsorption of calcium and phosphate, increasing body calcium and phosphate. They also enhance bone remodeling resulting in increasing bone density [3]. These actions are mainly mediated by its binding to a nuclear receptor, vitamin D receptor (VDR). Lead may share with calcium the same metabolic pathways for its toxicokinetics. Thus, polymorphism of VDR may have effects on lead toxicokinetics [4, 5].

By using a variety of restriction enzymes, various polymorphisms are identified and investigated for their effects on calcium metabolism. In this study, we determined if vitamin D receptor polymorphisms is associated with blood lead in Thai workers exposed to lead.

Materials and methods

Workers in a battery plant situated in a suburban area of Bangkok were recruited to participate in this study. Blood samples were obtained during their routine semi-annual health screening for lead exposure. Participants were voluntary and written informed consent was obtained from each of them. The study was approved by the Ethics Committee on

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The blood samples were divided into two tubes. The first tube containing 3 mL of blood and 300 µL of 0.2 M EDTA was used for the VDR genotype analysis. The second one was an acid washed, heparinized tube. It contained 2 mL of fresh blood for blood lead level determination.

Their demographic data (age, smoking status, alcohol ingestion, length of employment and type of job) were collected. The types of job determined the magnitude of lead exposure, which was categorized into three groups, high, moderate, and low magnitude of exposure. The high magnitude of exposure included workers whose work stations, and jobs were likely to be exposed to lead such as lead powder, pasting, grid, casing, alloy formation and assembly department. The moderate magnitude of exposure included workers whose jobs were not in direct contact to lead, but their work stations were in the same plant such as technicians, house keepers and quality control personnel. The low magnitude of exposure comprised workers whose work was not related to lead and they mainly worked in a separate building in the same factory such as office workers.

Blood lead levels were determined with graphite furnace atomic absorption spectrometry as described in detail by Subramanian and Meranger [6].

Genotyping

Genomic DNA of subjects was extracted from peripheral leukocytes. The DNA segments of VDR gene were amplified and validated by polymerase chain reaction, restriction fragment length polymorphism (PCR-RFLP) method. Details of each polymorphism are as follows:

FokI polymorphism: Genomics for the FokI polymorphisms in exon 2 was determined by using the primers: 5'AGCTGGCCCTGGCACTGACTCTG 3' and 5'CCTCCTGCTCCTGTGGCTGTGAG 3'. The PCR was performed in a 25-µL reaction volume containing 1 µL of genomic DNA, 0.5 µL of 10 mM dNTP, 0.3 µL of 20 µM primer *FokI*-for, 0.3 µL of 20 µM primer *FokI*-rev, 1.5 µL of 50 mM $MgCl_2$, 2.5 µL of 10X reaction buffer, 0.1 µL 5 U/µl of *Taq* DNA polymerase, and 19.4 µL ddH_2O. The running conditions were: pre-denature at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for one minutes, annealing at 70°C for one minutes, and extension at 72°C for one minutes. A final extension was at 72°C for10 minutes. The size of PCR product is 350 bp. These resulting 350-bp products were digested with FokI restriction nuclease. The "f" genotype shows the presence of restriction sites whereas the "F" genotype shows the absence and yields one digested band of the same size of PCR product. Genotype ff homozygote generates fragments of 280 and 70 bp. Genotype Ff heterozygote generates fragments of 350, 280, and 70 bp. Genotype FF homozygote contains a non digested 350 bp fragment

BsmI polymorphism: Genomics for the BsmI polymorphism in intron 8 were determined by using the primers: 5' AAGACTACAAGTACCGCGTCA GTGA 3' and 5' GGCAGAACCATCTCTCAGGCTC 3'. The PCR was performed in a 25 µL of reaction volume containing 1 □L genomic DNA, 0.5 µL of 10 mM dNTP, 0.3 µL of 20 µM primer *BsmI*-for, 0.3 µl of 20 µM primer *BsmI*-rev, 1.5 µL of 50 mM $MgCl_2$, 2.5 µL of 10X reaction buffer, 0.1 µL 5 U/µl of *Taq* DNA polymerase, and 19.4 µL ddH_2O. The running conditions were: holding at 95°C for five minutes, then 35 cycles of denaturation at 95°C for one minute, annealing at 67.3°C for one minutes, and extension at 72°C for one minute. A final extension was at 72°C for 10 minutes. The size of PCR product is 753 bp. The resulting 735-bp products were digested with BsmI restriction nuclease. The "b" genotype shows the presence of restriction sites whereas the "B" genotype does not but yields one-digested band of the same size of PCR product. Genotype bb homozygote generates fragments of 642 and 111 bp. Genotype Bb heterozygote generates fragments of 753, 642, and 111 bp. Genotype BB homozygote contains a non-digested 753 bp fragment.

ApaI and TaqI polymorphism: Genotypes for ApaI and TaqI polymorphism in intron 8 were determined by using the primers:

5'CAGAGCATGGACAGGGAGCAA3' and 5' TAGGCAGCGGTGGAGGCATCTCT 3'.

The PCR was performed in a 25 µL of reaction volume containing 1 µL of genomic DNA, 0.5 µL of 10 mM dNTP, 0.3 µL of 20 µM primer *Apa&Taq*-for, 0.3 µl of 20 µM primer *Apa&Taq*-rev, 1.5 µL of 50 mM $MgCl_2$, 2.5 µL of 10X reaction buffer, 0.1 µL 5 U/µL of *Taq* DNA polymerase, and 19.4 µL ddH_2O. The running conditions were pre-denaturation at 95°C for five minutes, then 35 cycles of denaturation at 95°C for one minutes, annealing at 69°C for one minutes, and extension at 72°C for one minutes. A final extension

was at 72°C for 10 minutes. The size of PCR product is 831bp. The resulting 831-bp products were digested with ApaI and TagI restriction nucleases, respectively. For ApaI polymorphism, the 'a' genotype shows the presence of restriction sites whereas the 'A" genotype does not but yields one digested band of the same size of PCR product. Genotype aa homozygote generates fragments of 614 and 217 bp. Genotype Aa heterozygote generates fragments of 831, 614, and 217 bp. Genotype AA homozygote contains a non digested 831 bp fragment. For TaqI polymorphism, genotype TT homozygote generates fragments of 494 and 337 bp. Genotype Tt heterozygote generates fragments of 494, 337, 293, and 201 bp. Genotype tt homozygote contains a digested 337, 293, and 201 bp fragments.

Cdx2 polymorphism: For the study of genotype of Cdx polymorphism in the promoter region, two sets of oligonucleotide primers of ASM-PCR were used:

G-For: 5' AGGATAGAGAAAATAATAGAAA ACATT 3'

G-Rev: 5' AACCCATAATAAGAAATAAGTT TTTAC 3'

A-For: 5' TCCTGAGTAAACTAGGTCACAA 3'

A-Rev: 5' ACGTTAAGTTCAGAAAGATTAA TTC 3'

The PCR was performed in a 20-µL reaction volume containing 0.2 µL of genomic DNA, 8 µL of master mix, 0.4 µL G-For and 0.4 µL A-Rev of 20 µM primer *Cdx*-2, 0.6 µL G-Rev and 0.6 µL A-For of 20 µM primer *Cdx-2*, and 9.8 µL ddH_2O. The running conditions were: pre-denaturation at 95°C for five minutes, then 35 cycles of denaturation at 95°C for one minute, annealing at 64.5°C for one minute, and extension at 72°C for one minute. G-Rev and A-For are allele-specific primers. The primer A-For is designed from 5' to 3' of the sense strand, and the last base is "A" at the site of the polymorphism. The primer G-Rev is from 5' to 3' of the antisense strand, and stops at "C" (the complement base of "G") at the polymorphic site. These four primers generate three PCR fragments: primers set G-For and G-Rev specifically amplify the G allele with a size of 110 bp, A-For and A-Rev specifically amplify the A-allelle with a size of 235 bp, and the out-primer pair (G-For and A-Rev) amplifies the internal control PCR fragment with a size of 297 bp.

The Cdx-2 was characterized as a 297-bp fragment. The 23- bp fragment is the "A" allele specific PCR product whereas the 110-bp fragment is the "G" allele specific fragment. Genotype AA homozygote generates fragments of 297 and 235 bp. Genotype AG heterozygote generates fragments of 297, 235, and 110 bp. Genotype GG homozygote contains 297 bp and 110 bp fragments.

Data analysis

Statistical analysis was carried out using SPSS version 11.5. All probabilities used the 2-tailed test and statistically significant level at p-value of 0.05. Chi-square test for goodness of fit was used for the determination of VDR genotypes by Hardy-Weinberg law [7]. Comparison t-test and ANOVA were used to find the difference between or among the groups. The Kruskal-Wallis test was used for determining the difference of blood lead level among the genotypes of BsmI and TaqI polymorphisms. Correlations between blood lead level and various factors including vitamin D Receptors were determined by regression analysis.

Results

Four hundred fifteen lead-exposed workers (343 men and 72 women) participated voluntarily in the study. Their demographic data are shown in **Table 1**.

Proportion of women working in the low exposure condition was higher than men. Women also had lower percentage of smoking, alcohol consumption, and shorter length of employment. It was apparent from **Table 2** that gender, smoking, alcohol consumption, and lead exposure status were the factors that could cause variability of blood lead levels.

Table 3 shows their genotypes. All genotype distributions of these polymorphisms were in the Hardy-Weinberg equilibrium. The allele frequencies of F/f, B/b, A/a, T/t and A/G for the FokI, BsmI, ApaI, TaqI and Cdx2 polymorphisms were 0.59/0.41, 0.07/0.93, 0.32/0.68, 0.94/0.06, and 0.4/0.6, respectively.

Table 4 shows comparison of mean blood lead levels with Cdx-2, FokI, and ApaI genotypes by one way ANOVA. We found no difference in the blood lead levels among different genotypes in Cdx-2, FoxI, and ApaI genes.

Table 5 shows comparison of blood lead levels with BsmI and TaqI genotypes by Kruskall-Wallis test. We found that homozygous BB of BsmI and homozygous tt of TaqI genes had significantly lower blood lead levels than other genotypes (P=0.02 and 0.03, respectively).

Table 1. Demographic data of 415 subjects.

Characteristics	Female (N=72)	Male (N=343)
Age (years, mean±SD)	31.36±9.32	32.85±8.15
Weight (kg, mean±SD)	54.51±9.19	61.76±10.46
Height (kg)	158.74±6.55	167.75±6.24
Length of employment (years, mean±SD)	6.89±7.59	9.02±9.13
Lead exposure status, number (%)		
Low exposure	17 (23.6)	9 (2.6)
Moderate exposure	9 (12.5)	67 (19.5)
High exposure	46 (63.9)	267 (77.9)
Smoking status, number (%)		
Non smoker	72 (100)	184 (53.6)
Smoker	0 (0)	159 (46.4)
Alcohol consumption, number (%)		
No	67 (93.1)	85 (24.8)
Yes	5 (6.9)	258 (75.2)

Table 2. Comparison of mean blood lead levels with different subject characteristics.

Characteristics	Number	Blood lead levels (μg/dL)	
		Mean±SD	Range
Gender			
female	72	28.71±13.08	7.0-57.0
male	343	39.15±12.16[a]	9.0-82.0
Age (years)			
<25	88	38.92±13.04	13.0-82.0
>25-30	123	37.23±13.03	9.0-74.0
>30-35	88	38.07±12.68	7.0-65.0
>35-40	52	38.19±9.67	17.0-61.0
>40-45	20	30.15±12.07	10.0-54.0
>45	44	35.27±15.85	7.0-63.0
Smoking status			
non-smoker	256	34.95±13.15	7.0-71.0
smoker	159	41.18±11.62[b]	11.0-82.0
Alcohol consumption			
non drinker	152	33.24±12.99	7.0-63.0
drinker	263	39.7±12.32[c]	9.0-82.0
Exposure status			
high exposure	255	39.75±11.34	11.0-82.0
moderate exposure	67	34.05±13.8[d]	12.0-63.0
low exposure	21	17.81±9.49[e]	7.0-46.0

[a]Significantly different from females ($P<0.05$), [b]significantly different from nonsmokers ($P<0.05$), [c]significantly different from non drinkers ($P<0.05$), [d]significantly different from moderate and low exposure status ($P<0.05$), [e]significantly different from high and low exposure status ($P<0.05$).

Table 3. Genotype and allele frequency of 5 VDR polymorphisms.

	Genotype frequency (%)			P-value	Allele frequency	
Fok I	**FF**	**Ff**	**ff**		**F**	**f**
	36.9	44.3	18.8	0.24	0.59	0.41
Bsm I	**BB**	**Bb**	**bb**		**B**	**b**
	0.7	13.5	85.8	0.56	0.07	0.93
ApaI	AA	Aa	aa		A	a
	10.6	42.4	47.0	0.89	0.32	0.68
TaqI	**TT**	**Tt**	**tt**		**T**	**t**
	89.2	10.1	0.7	0.32	0.94	0.06
Cdx-2	**AA**	**AG**	**GG**		**A**	**G**
	16.6	47.7	35.7	0.94	0.40	0.60

P-value>0.05 indicates no deviation from Hardy-Weinberg equilibrium.

Table 4. Comparison of mean blood lead levels with Cdx-2, FokI, and ApaI genotypes by one way ANOVA.

Genotype	Number	Blood lead levels (μg/dL)	
		(Mean±SD)	Range
FokI			
FF	153	36.63±13.64	7.0-67.0
Ff	184	37.49±11.97	11.0-74.0
ff	78	38.35±13.76	9.0-82.0
ApaI			
AA	44	36.05±13.40	7.0-62.0
Aa	176	38.45±13.05	7.0-82.0
aa	195	36.62±12.70	7.0-63.0
Cdx-2			
AA	69	38.39±12.10	9.0-63.0
AG	198	37.05±13.21	11.0-82.0
GG	148	37.22±12.98	7.0-63.0

Table 5. Comparison of blood lead levels with BsmI and TaqI genotypes by Kruskrall-Wallis test.

Genotype	Number	Blood lead levels (μg/dL)			
		Median	Range	Mean Rank	P-value
BsmI					
BB	3	14.0	7.0-20.0	21	0.02
Bb	56	36.5	13.0-74.0	198.69	
bb	356	38.0	7.0-82.0	211.04	
TaqI					
TT	370	38.0	7.0-82.0	210.87	0.028
Tt	42	37.0	7.0-67.0	195.27	
tt	3	19.0	14.0-20.0	32.17	

By regression analysis, gender, smoking status, and lead exposure status consistently showed correlations with the blood lead levels. Male, smoker, and high exposure status groups had higher blood lead level than others in their groups. For genetic alleles, all five polymorphisms were tested by regression analysis. It seemed that only TaqI and BsmI polymorphism might affect the blood lead level, as shown in **Tables 6** and **7**, respectively. This was consistent with the one way ANOVA in **Tables 4** and **5**. The homozygous tt had lower blood lead level than homozygous TT (P=0.00). For BsmI polymorphism, the homozygous BB had lower blood lead level than homozygous bb (P=0.01).

Table 6. The association between potential factors including BsmI polymorphism and blood lead levels as determined by regression analysis.

Dependent variable	**Blood lead level (μg/dL)**		
Independent variables	**β coefficient**	**Standard error**	**P-value**
Age	-0.168	0.128	0.18
Gender (male/ female)	-4.698	1.88	0.01
Smoking (smoker/ non-smoker)	2.789	1.294	0.03
Alcohol (drinker/ non drinker)	1.482	1.487	0.32
Exposure status			
high/ low exposure	16.976	2.486	0.00
moderate/ low exposure	11.576	2.733	0.00
VDR genotype: BsmI			
Bb/ bb	-1.108	1.648	0.50
BB/ bb	-17.192	6.632	0.01
Intercept	25.391	5.23	0.00
R^2 (adjusted)=0.253			

Table 7. The association between potential factors including TaqI polymorphism and blood lead levels as determined by regression analysis.

Dependent variable	**Blood lead level (μg/dL)**		
Independent variables	**β Coefficient**	**Standard error**	**P-Value**
Age	-0.17	0.127	0.18
Gender (male/ female)	-4.853	1.876	0.01
Smoking (smoker/ non-smoker)	2.635	1.286	0.04
Alcohol (drinker/ non drinker)	1.56	1.481	0.29
Exposure status			
high/ low exposure	17.578	2.467	0.00
moderate/ low exposure	12.368	2.725	0.00
VDR genotype: TaqI			
Tt/ TT	-1.68	1.856	0.36
Tt/ TT	-19.512	6.607	0.00
Intercept	24.726	5.214	0.00
R^2 (adjusted)=0.257			

Discussion

The present study showed that allele frequencies of the polymorphisms were BsmI, ApaI, TagI, Cdx-2, and FokI. These allele frequencies agree with those reported in the previous studies in Thai population and the Asians [8]. For Cdx-2 [9] and FokI polymorphism [10], the allele frequencies were similar to other Asian populations. However, the allele frequencies of all five polymorphisms were different from those of the Caucasians.

Blood lead level is a practical biomarker for lead exposure and internal dose of lead. Body burden of lead may be influenced by both environmental and internal factors. The present study showed that an environmental factor, which is "magnitude of exposure", was the strongest factor contributing to the blood lead level. This has been consistently found in our previous studies [11, 12]. Smoking and gender were two internal factors affecting lead level. Smoking is a known-acquired factor causing elevation of blood lead level [13-16] because cigarette and tobacco contain lead [17]. For gender factor, our study showed that males had higher blood lead levels than females. This is consistent with those reported by many previous studies [18-22].

The present study focused on effect of TaqI and Cdx2 polymorphisms on the lead level. Previous studies mostly focused on BsmI, ApaI, and FokI [5, 23, 24] and yielded conflicting results [24-26]. Our study showed that subjects of the tt genotype for the TaqI polymorphism and BB genotype for BsmI polymorphism had lower blood lead level than those of other genotypes. The BB genotype with lower blood lead than the bb genotype is different from a previous study [27].

Although the mechanisms of the polymorphisms of vitamin D receptor gene on the function of vitamin D remain unknown, several lines of evidence indicate that the BB genotype of BsmI polymorphism may be associated with decreasing calcium absorption, increasing bone loss, and decreasing body mineral density [28, 29]. The tt genotype of TaqI polymorphism is also associated with decrement of body mineral density in both young women and osteoporosis patients [1, 25]. Our finding may support the postulation that lead may follow the biological pathways of other bivalent cations such as calcium and iron. They may compete for absorption and protein binding. Wright et al. [30] reported that dietary calcium and iron were inversely associated with lead absorption [30]. Our finding and postulations may support previous suggestions. If this postulation is valid, modulation of calcium metabolism may eventually be a venue to prevent lead absorption and decrease lead body burden.

In conclusion, BsmI and TaqI polymorphisms of vitamin D receptor gene were the additional intrinsic factors that had impact on the blood lead level. The BB genotype of BsmI and the tt genotype of TaqI had lower blood lead levels than other genotype groups.

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The authors declare no conflict of interest in conducting this study.

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