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A dopamine receptor (DRD2) but not dopamine transporter (DAT1) gene polymorphism is associated with neurocognitive development of Mexican preschool children with lead exposure

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Abstract

Objective—To investigate the effects of pre- and postnatal lead exposure and polymorphisms in dopamine metabolism genes on neurocognitive development of Mexican children at 24 (n=220) and 48 months (n=186) of age.

Study design—We genotyped the dopamine transporter gene (*DAT1*; *SLC6A3*) variable nucleotide tandem repeat, and the dopamine receptor D2 (*DRD2*) *Taq IA* single nucleotide polymorphism. Children were assessed at 24 mo with Bayley Scales of Infant Development (MDI, PDI) and at 48 mo with McCarthy Scales of Children's Abilities.

Results—Lead concentration (BLL) in umbilical cord was 6.6 ± 3.3 $\mu\text{g/dL}$ (measured in 1995-96), 8.1 ± 4.4 $\mu\text{g/dL}$ at 24, and 8.1 ± 3.6 $\mu\text{g/dL}$ at 48 months. Cord BLL was negatively associated with MDI ($p < 0.01$) and PDI ($p < 0.1$) but not McCarthy scores. The 48- but not 24-month BLL was negatively associated with children's scores. Children with *DRD2 TT* genotype (variant) scored higher than those with *CC* genotype (wild type) on MDI and McCarthy memory scale. Neither polymorphism modified the relationship between BLL (either pre or post-natal) and neurocognitive development.

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The authors declare no conflicts of interest.

Conclusion—Lead exposure was adversely, whereas the *DRD2 Taq IA* TT variant was positively associated with neurocognitive measures. We found no evidence of gene-environment interactions on developmental outcomes in early childhood.

Keywords

Cord blood lead; postnatal lead exposure; DAT1; DRD2; gene polymorphisms; Mexico; child development

Lead exposure is associated with behavioral and cognitive deficits in children (1). Impairments in executive function are one of the hallmark effects, even at low levels (2, 3), and suggest the involvement of dopamine neurotransmission (4-7). Altered dopamine metabolism and polymorphisms in dopamine-related genes have also been associated with behavioral manifestations in children (8, 9). Whereas the contribution of these polymorphisms to attention deficit hyperactivity disorder is established (8), less is known about their relationship to cognition, particularly in children exposed to environmental toxicants.

Several genes mediate dopaminergic neurotransmission, and at least 2 have putatively functional variants, including genes encoding the dopamine transporter (DAT1) and dopamine receptor-2 (DRD2). The DAT1 clears dopamine from synapses (10) and limits the duration of synaptic activity (11). A variable number tandem repeat (VNTR) polymorphism of the *DAT1* gene (*SLC6A3*) is well studied (12) and its length is thought to relate to DAT expression (13) and availability (14), with higher expression and availability being found in individuals with 10- vs. 9-repeat VNTR. In turn, the DRD2 regulates neurotransmission via a feedback loop, and a polymorphism in the *DRD2 Taq IA* gene (specifically the variant carrier vs. wild type genotype) is linked with reduced D2 receptor density and availability (15, 16).

The existing studies on the relationship between *DAT1* and cognition are inconsistent: two showed an association with selective attention (17) and IQ in children with ADHD (18), and one found no relationship (19). Conversely, *Taq IA* was not independently associated with IQ (20-22). None of these studies were designed to evaluate gene-environment interactions. However, there is growing evidence (3, 23) that dopamine metabolism is related to the effects of environmental exposures, and specifically lead (24), suggesting that dopamine gene polymorphisms could modify an individual's vulnerability to lead exposure. This potential interaction between lead exposure and dopamine gene polymorphisms needs to be addressed in population studies.

Our group has previously shown that prenatal exposure to lead was associated with global indices of development in young children (25). Here we investigated whether the association between lead exposure (pre- and postnatal) and neurocognitive development of Mexican children at 24 and 48 months of age is modified by polymorphisms in *DAT1* and *DRD2* genes.

METHODS

Pregnant women receiving antenatal care between January 1994 and June 1995 at three hospitals that serve low-to-middle-income Mexico City populations were invited to participate. The study population, eligibility criteria and recruitment have been described previously (26). A total of 617 women were enrolled and their infants were eligible to participate in a child development study. The study was approved by ethics review boards at the National Institute of Public Health in Mexico, National Institute of Perinatology in

Mexico, Brigham and Women's Hospital, Harvard School of Public Health, and participating hospitals.

Demographic and maternal characteristics were collected using questionnaires. Newborn characteristics were obtained from medical records, whereas anthropometric measurements were collected within 12 hours of delivery. Umbilical cord blood samples were collected at delivery. Blood lead concentration (BLL) was measured using graphite furnace atomic absorption spectrometry (Model 3000: Perkin Elmer, Wellesley, MA USA) at the American British Cowdray Hospital Trace Metal Laboratory in Mexico City according to established techniques (27). The laboratory participates in the Centers for Disease Control and Prevention (CDC) blood lead proficiency testing program, and maintained acceptable precision and accuracy over the study period. The limit of detection was 0.8 µg/dL.

Archived cord blood samples were used for DNA extraction and genotyping at the Harvard-Partners Center for Genetics and Genomics (Boston, MA). High-molecular-weight DNA was extracted from white blood cells (PureGene Kits, Gentra Systems, Minneapolis MN), yielding 20–40 µg of DNA per mL whole blood. After DNA quantification, samples were adjusted to TE buffer and stored at –80°C. TaqMan platform was used to genotype dopamine receptor D2 *Taq IA* SNP (rs1800497) and the 3' *VNTR* at the dopamine transporter gene (*SLC6A3*). Ninety seven percent of samples with adequate DNA concentration were successfully genotyped.

Children's development was assessed at 24 months of age using the Bayley Scales of Infant Development II (BSID-II) and at 48 months of age using the McCarthy Scales of Children's Abilities (McCarthy). The BSID-II yields the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). The McCarthy yields several sub-scales, including the General Cognitive Index (GCI) and the memory scale, which we used as dependent variables in this study. Assessments were conducted in Spanish by psychologists at the Department of Developmental Neurobiology, National Institute of Perinatology in Mexico City.

Of the 617 children evaluated at delivery, 62 were excluded from analysis because of missing information on polymorphisms, marital status, mother's IQ, schooling and smoking, birth weight and gestational age; 94 did not have cord BLL data. At 24 months, 211 children did not return for developmental testing and 30 did not have a BLL value. At 48 months, another 19 were missing maternal IQ and polymorphism data, 221 children did not return for developmental testing and 35 did not have a BLL value. Complete information was available on 220 and 186 children at 24 and 48 months, respectively.

Data were analyzed using STATA 10.0 (STATA Corp, College Station, TX). Genotype frequencies were calculated and compared against expected counts using the chi-square statistic to test adherence to the principles of Hardy–Weinberg equilibrium. For the *DAT1*, children with 10-repeat VNTRs in both alleles were compared with children with any 9-repeat alleles. For the *DRD2*, children with CT and TT genotypes were compared with the wild type genotype (CC). In regression models we investigated: 1) whether pre- and postnatal lead exposure was associated with child development; 2) whether dopamine gene polymorphisms were associated with child development; and 3) whether dopamine gene polymorphisms modified the relationship between pre- or postnatal lead exposure on child development. First (Model 1), we addressed the question of whether BLLs were independently associated with developmental scores. Ordinary least squares (OLS) multiple linear regression models examining the association between developmental outcomes and pre- and postnatal lead exposure were conducted separately for the 24 (MDI and PDI) and 48 (GCI & memory scale) month measures. The models were adjusted for relevant

covariates. Subsequently, the developmental outcomes were modeled as a function of each polymorphism separately, adjusting for relevant covariates (Models 2 & 3).

Finally, we modeled cord and postnatal BLL with each polymorphism to predict child performance at 24 and 48-months, testing for 2-way interactions (BLL \times polymorphism). Interactions between dopamine gene polymorphisms and cord BLL were tested in separate models from interactions between the polymorphisms and postnatal BLLs. Non-significant interactions ($p > 0.10$) were removed and regression models were re-run to test for main effects of lead exposure and polymorphism. All regression models were adjusted for: gestational age, birth weight, child sex; mother's IQ, years of education, age, smoking, marital status at enrollment; crowding in the house (bedrooms divided by number of people living in the house), and type of floor (wood/mosaic or concrete; used as a proxy for socioeconomic status).

RESULTS

There were no meaningful differences between children included in the analysis and those who were excluded, either at 24 months (Table I) or 48-months (data not shown). At delivery, 13.6% of the children had cord BLLs ≥ 10 $\mu\text{g}/\text{dL}$. At 24 months, children's mean BLL was 8.1 ± 4.4 $\mu\text{g}/\text{dL}$ (Table I), and 23.2% had BLLs ≥ 10 $\mu\text{g}/\text{dL}$. In turn, the mean BLL of the children at 48 months was 8.1 ± 3.6 $\mu\text{g}/\text{dL}$, with 21.0% having BLLs ≥ 10 $\mu\text{g}/\text{dL}$. The mean MDI score at 24 months was 91.3 ± 14.2 points (Table I) and the mean score on the McCarthy Scales GCI at 48 months was 94.1 ± 13.3 points.

For the *Taq IA*, 52.6% of children had a *CT* genotype and 21.9% had the *TT* genotype, with variant allele frequency of 0.49. For *DAT1*, 80.8% of children had two copies of the 10-repeat allele typically associated with higher gene expression, whereas 19.1% of the children had at least one 9-repeat allele. The alleles for both gene polymorphisms were in Hardy-Weinberg equilibrium. For combined genotypes, 20.2% of the sample had wild type genotype for the *DRD2* gene (*CC Taq IA* genotype) together with the 9-repeat VNTR for *DAT1*. In turn, 20.4% of the children had the 10-repeat *DAT1* alleles and the *TT Taq IA* (variant) genotype.

Are blood lead concentrations associated with cognitive performance?

Cord blood lead concentrations were negatively associated with 24-month MDI scores (Table II, Model 1). Specifically, each $1\mu\text{g}/\text{dL}$ of cord BLL was associated with MDI scores being lower by 0.7-points ($p < 0.05$). BLL measured at 24 months was not statistically associated with MDI or PDI scores (Table II, Model 1). When adjusted for the 48-month BLLs and covariates, cord BLL was not associated with the McCarthy Scales scores. BLL measured at 48 months was inversely associated with McCarthy GCI ($p < 0.05$) and memory scores ($p < 0.1$).

Are polymorphisms in dopamine metabolism genes associated with cognitive performance?

The 10-repeat VNTR of the *DAT1* gene was not associated with cognitive performance at either 24 or 48 months (Table II, Model 2). On the other hand, children with the variant (*TT Taq IA*) genotype scored significantly higher than children with the *CC* genotype on the 24-month MDI and the 48-month McCarthy memory sub-scale (Table II, Model 3). There were no interactions between *DAT1* and *DRD2* on cognitive performance.

Does *DRD2* or *DAT1* modify the association between BLL and cognitive performance?

There were no statistically significant interactions between cord BLL and *DRD2* or *DAT1* on the 24-month MDI or PDI scores. When the analysis was repeated testing the main effects model, cord BLL significantly predicted MDI scores when entered together with the *DAT1* into the regression model (Table III). Cord BLL ($p < 0.1$) was also independently associated with children's PDI scores when modeled together with *DAT1*. However, the 10-repeat VNTR of the *DAT1* gene was not associated with MDI or PDI scores. The *DRD2 TT* genotype independently predicted children's 24-month MDI scores. Furthermore, neither the *DRD2* nor the *DAT1* genotype modified the association between 24-month BLL and the MDI or PDI (data not shown).

Neither the *DRD2 Taq1A* nor the *DAT1* 10-repeat VNTR modified the association between cord blood lead level and children's performance on the McCarthy GCI or memory sub-scale. When the analyses were repeated testing for main effects of BLL and dopamine genotypes, cord BLL was not a significant predictor of the 48-month developmental outcomes when either gene was entered into the regression model (Table III). The 10-repeat VNTR of the *DAT1* was also not associated with GCI or memory sub-scale of the McCarthy Scales in main effects models (Table III). The *DRD2 Taq1* was not related to GCI scores. However, when adjusted for covariates and cord BLL, *DRD2 TT* genotype was associated with higher memory scores at 48 months (Table III). There were no significant statistical interactions between the *DRD2* and the *DAT1* on the two McCarthy scale measures (data not shown). Finally, neither the *DRD2* nor the *DAT1* genotype modified the association between 48-month BLL and the 48-month outcomes—the slopes of the relationship between 48-month BLL and neurocognitive outcomes did not differ by *DRD2* genotype (*CC*, *CT* or *TT*; data not shown).

DISCUSSION

A strong body of evidence suggests that, in addition to postnatal exposure, maternal or cord blood lead levels are associated with poorer cognitive outcomes (28-30). Our study demonstrates that cord BLLs are associated with global measures of child development at 24 months of age, independently of the exposures that occurred in the postnatal period. This relationship was not apparent at 48 months of age, possibly because with longer postnatal exposure the influence of prenatal BLL on brain structure and the development of cognitive competencies becomes less influential. In fact, BLL measured at 48 months of age was statistically associated with lower GCI and memory scores of the McCarthy Scales administered at 48 months of age. Although cord BLLs were higher in our sample than in other groups [0.44–6.90 $\mu\text{g/dL}$ in Polish newborns (31) and 0.2–9.7 $\mu\text{g/dL}$ in Inuit newborns (28)], our findings are consistent with those reports.

Second, we investigated the interaction between BLLs and two gene polymorphisms. We found that although the *TT* genotype of the *DRD2* was positively associated with MDI and memory scores, it did not modify the association between cord BLL (or BLL measured postnatally) and child development. The *DAT1* was not associated with child development in lead exposed children and did not modify the relationship between lead exposure and neurocognitive measures used in this study. The majority of other studies that examined the effects of lead exposure on children's development have not investigated potential effect modification due to genetic variability.

Lead exposure in children has been associated with dopamine-related cognition including executive functioning (2, 3) and behavior problems including ADHD (32). Lead affects several aspects of dopamine neurotransmission, in a dose-related and brain region-specific manner (5). The effects include changes in dopamine metabolism, release, and reuptake by

DAT (5). There is evidence of increased D2 receptor sensitivity after postnatal (4) and prenatal (6) lead exposure. In addition, moderately elevated BLLs (~15µg/dL) are associated with synaptic dopamine overflow in the nucleus accumbens (7).

Dopaminergic neurotransmission is also affected by gene polymorphisms. The majority, 80.8%, of children in this study had the 10-repeat VNTR of the *DAT1*. Approximately 20% of the sample had at least 9-repeat VNTRs. This is consistent with previous work, which shows that the 10-repeat VNTR allele occurs frequently in various populations (33). The 10-repeat VNTR of the *DAT1* is associated with increased DAT expression (13) and availability (14), whereas the *Taq IA* polymorphism has been associated with reduced D2 receptor density (15, 16). The functional implications of this are still unclear for populations exposed to toxicants that affect dopamine signaling. We did not observe statistical interactions between children's BLLs and dopamine gene polymorphisms and cannot speculate on the potential mechanisms that would drive the combined effects of lead exposure and dopamine gene polymorphisms on neural functioning or child development. In another study of school children, those with variant *DRD2 Taq IA* genotype experienced a stronger deficit in IQ scores for each unit increase in BLLs measured concurrently to the IQ test than children with wild type genotype (24), although the lead × *DRD2* interaction term was not statistically significant.

Our study failed to document significant lead × *DRD2* interactions but Roy et al suggest that reduced D2 receptor density is associated with worse outcomes in lead-exposed children (24). Because we did not observe effect modification by dopamine genes either with prenatal or postnatal exposure, the possibility of the differential findings between our study and that of Roy et al being due to differences in the timing of exposure is not likely. Rather, differences between these two studies could be due to differences in the severity of lead exposure (BLL [mean±SD]: 11.5±5.3 µg/dL among Indian children and 8.1±4.4 µg/dL in our study). In addition, the developmental measures employed to assess preschool children in our study are thought to correlate poorly with the types of cognitive and IQ assessments used in school-age children by Roy et al (24). It is possible that the two studies are assessing different cognitive domains, particularly because many functions contributing to IQ, such as attention, follow a developmental trajectory and mature during the school years. Finally, our measures may not be sensitive to lead-induced damage to the prefrontal cortex, which subserves the executive functions we hypothesized could link the dopaminergic system and lead exposure to IQ deficits.

Our study had some limitations. First, the analysis was based on a modest sample size. It is possible we did not have the appropriate statistical power to detect interactions between prenatal lead exposure and dopamine gene polymorphisms. However, in another examination of gene-environment interactions in this cohort, Cantonwine et al found effect modification between *HFE* gene polymorphism and cord BLL on birth weight (34). In a sample of 174 children, interactions were also found between child's *DRD4* polymorphism, BLL and executive function (3). These studies suggest that with the sample sizes used here, gene-environment interactions are detectable. Our limited sample size was due to participant attrition. Because we found no significant differences in demographic characteristics between study participants and those excluded from analysis, we believe the findings accurately represent the relationship between lead exposure and measures of child development in the target population. The exclusion of children reflects the difficulty of prospectively following a large cohort of participants who have multiple assessments and visits over time, and does not appear to reflect a systematic bias (Table I). Nevertheless, a larger sample size would likely clarify the effects of the *DRD2* polymorphism on the developmental measures, where children with the *TT* genotype performed better on the MDI but not the PDI at 24 months and better on the memory sub-scale but not on GCI at 48

months. We also had limited ability to account for children's home environment, an important determinant of child development. Some factors that influence the home environment include maternal IQ and marital status, physical characteristics and crowding in the house. We accounted for these and other potentially influential factors in our analysis.

In summary, an index of prenatal lead exposure was adversely associated with global measures of child development at 24 but not 48 months of age, independently of the influence of postnatal lead exposure. We also found independent positive associations between *DRD2* polymorphisms and global measures of child development. However, we found no evidence of gene-environment interactions where dopamine gene polymorphisms modify the effect of lead exposure, either measured pre or postnatally, on neurocognitive outcomes in young children. In light of contrasting results in other populations, further studies of this kind are warranted.

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Table 1

Sample characteristics.

	Included at 24 months	Excluded at 24 months
<u>Household characteristics</u>		
Years in Mexico	21.1 ± 7.7 ¹	20.3 ± 8.6
Crowding, persons/bedroom	3.3 ± 1.6	3.4 ± 1.6
<u>Maternal characteristics</u>		
Age at enrollment, y	24.5 ± 5.0	24.7 ± 5.3
BLL at delivery, µg/dL	8.6 ± 4.0	8.5 ± 4.5
Married	66.4%	66.6%
IQ score	84.4 ± 22.5	85.0 ± 25.0
<u>Child characteristics</u>		
Birth weight, g	3176 ± 413	3127 ± 414
Boys	51.8	54.6
Cord BLL, µg/dL	6.6 ± 3.3	6.6 ± 3.7
≥ 10	13.6%	12.9%
Concurrent BLL, µg/dL	8.1 ± 4.4	8.4 ± 4.3
≥ 10	23.2%	30.4%
MDI score	91.3 ± 14.2	92.8 ± 13.9

¹Values given as M ± SD or %.

Table 2

Associations between lead exposure, *Taq 1A*, and *SLC3A6* polymorphisms and measures of child development at 24 and 48 months of age.

	24 months ¹		48 months ⁵	
	MDI	PDI	GCI	Memory score
<u>Model 1—BLL</u>				
Cord BLL	-0.7 ± 0.3 ^{2**}	-0.4 ± 0.2	-0.2 ± 0.3	0.01 ± 0.1
Concurrent BLL ³	-0.1 ± 0.2	-0.2 ± 0.2	-0.6 ± 0.2 ^{**}	-0.3 ± 0.1 [*]
<u>Model 2—<i>SLC6A3</i></u>				
Any 9-repeat alleles	---	---	---	---
Both 10-repeat alleles	-2.9 ± 2.4	-2.4 ± 2.2	-3.1 ± 2.4	-1.7 ± 1.3
<u>Model 3—<i>Taq 1A</i></u>				
CC	---	---	---	---
CT	2.0 ± 2.2	0.6 ± 2.1	-0.7 ± 2.2	0.4 ± 1.2
TT	6.5 ± 2.8 ^{**}	-0.3 ± 2.6	2.5 ± 2.6	3.4 ± 1.4 ^{**}

¹ MDI—mental development index; PDI—psychomotor development index; Adjusted for birth weight, gestational age, child sex; maternal age, years of schooling, IQ, smoking (ever), marital status at enrollment; crowding in the house, type of floor in the house; n=216;

² Values given as $\beta \pm SE$;

³ Concurrent BLL—blood lead level measured at the time of neurocognitive testing (at 24 months for MDI and PDI; at 48 months for GCI and memory test);

⁴ comparison group;

⁵ GCI—General Cognitive Index; consists of verbal, performance and quantitative sub-scales; Adjusted for child sex, birth weight, gestational age; maternal age, years of schooling, IQ, smoking (ever), marital status at enrollment; crowding in the house, type of floor in the house, n=186;

* p<0.1;

** p<0.05.

Table 3

The main effects of lead exposure and dopamine gene polymorphisms on measures of child development at 24 and 48 months of age.

	MDI ^{1,2,3}	PDI ^{1,2,3}	GCI ^{1,2,5}	Memory ^{1,2,5}
Cord BLL	-0.7 ± 0.3**	-0.5 ± 0.2*	-0.2 ± 0.3	-0.01 ± 0.1
Concurrent BLL ⁶	-0.1 ± 0.2	-0.1 ± 0.2	-0.5 ± 0.2**	-0.3 ± 0.1*
SLC6A3 – any 9-repeat VNTR	--- ⁴	---	---	---
Both 10-repeat VNTR	-3.8 ± 2.4	-3.0 ± 2.2	-3.3 ± 2.4	-1.7 ± 1.4
Cord BLL	-0.6 ± 0.3**	-0.4 ± 0.3*	-0.1 ± 0.3	0.04 ± 0.1
Concurrent BLL ⁶	-0.2 ± 0.2	-0.2 ± 0.2	-0.6 ± 0.2**	-0.3 ± 0.1**
Taq 1A – CC	---	---	---	---
CT	2.0 ± 2.2	0.7 ± 2.1	-0.7 ± 2.2	0.4 ± 1.2
TT	6.4 ± 2.8**	-0.4 ± 2.6	2.5 ± 2.6	3.4 ± 1.4**

¹ Values given as $\beta \pm SE$;

² Adjusted for maternal age, smoking (ever), total years of schooling, marital status at enrollment, IQ; child sex, gestational age, birth weight; crowding in the house, type of floor;

³ The regression model tests the main effects of BLL and dopamine gene polymorphism, after the polymorphism × BLL interaction terms had been tested and found to be non-significant;

⁴ Comparison group;

⁵ Adjusted for maternal age, smoking (ever), total years of schooling, marital status at enrollment; child sex, gestational age, birth weight; crowding in the house, floor type;

⁶ Concurrent BLL—blood lead level measured at the time of neurocognitive testing (at 24 months for MDI and PDI; at 48 months for GCI and memory test);

* p<0.1;

** p<0.05.