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Polymorphisms of delta-aminolevulinic acid dehydratase (ALAD) and peptide transporter 2 (PEPT2) genes in children with low-level lead exposure

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ABSTRACT

Low-level lead exposure during early childhood has long been associated with altered neurocognitive development and diminished cognitive functions. Over nine thousand U.S. industrial facilities annually emit significant amounts of lead, creating exposure risk particularly for minority children. The mechanisms by which low-level lead exerts neurotoxic effects are poorly understood. Once absorbed, the only intervention is source removal, thus primary prevention is key. Genetic biomarkers could provide an efficient means of identifying children at greatest risk. Common functional variants of genes that alter lead’s neurotoxic potential have been identified and include delta-aminolevulinic acid dehydratase (ALAD2) and peptide transporter 2 (PEPT2*2). These polymorphisms have not been examined previously in Hispanic minority samples, or with regard to lowest level lead exposure. In 116 children of Mexican-American/Hispanic descent residing in zip codes previously designated as “high risk” for lead exposure (mean age = 8.1, S.D. = 1.9), blood lead level was measured at three time points over a 3-month period and averaged. DNA extraction was completed using buccal swab samples. The frequencies of the ALAD2 and PEPT2*2 polymorphisms observed in this sample closely approximated those previously reported for Anglo, European and Asian samples. As compared to children heterozygous for the PEPT2*2 polymorphism, and without the PEPT2*2 polymorphism, the geometric mean blood lead level of children homozygous for the PEPT2*2 polymorphism was significantly higher. In contrast to past studies, mean blood lead level of children heterozygous and homozygous for the ALAD2 polymorphism in this sample did not differ from that of children without the ALAD2 polymorphism. Higher blood lead burden in children with the PEPT2*2 mutation may suggest that this common genetic variant is a biomarker of increased vulnerability to the neurotoxic effects of lowest level lead exposure.

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1. Introduction

1.1. Low-level lead exposure in children

Lead toxicity is diagnosed when a child’s blood lead level (BLL) is greater than 10 micrograms per deciliter (µg/dL), “Toxicity” as it is currently defined however is not the only threat posed by environmental lead. Exposure yielding detectable blood lead levels in children below 10 µg/dL have long been associated with diminished neurocognitive function resulting in poorer reading and math skills, and deficits in abstract reasoning and short-term memory (Workgroup, 2004; Lanphear et al., 2000). According to the most recent Environmental Protection Agency (EPA) inventory (2002), 9600 facilities across the United States annually emit from 1 to more than 10,000 pounds of lead per year. Other known sources of exposure include and are not limited to inhalation of lead paint dust and/or ingestion of lead paint chips in old housing, ceramic glaze, inexpensive cookware, paints used on children’s toys, children’s jewelry, and some candy imported from Mexico (CDCP, 2009). Lead exposure is overwhelmingly prevalent among minority children (Bernard and McGeehin, 2003) and low-level exposure is a risk for the nation’s most vulnerable children (Carter-Pokras and Baquet, 2002).

1.2. Genetic polymorphisms associated with increased risk of neurotoxicity

Lead is absorbed through both ingestion and inhalation, and is excreted in the urine and feces, and to a lesser extent, in sweat, nails and hair. In children, up to 50% of ingested lead, and up to 70% of inhaled lead, is absorbed into soft tissue, bone and the blood (Finkelstein et al., 1998). Lead enters red blood cells (Silbergeld et al., 1995).
et al., 2000) where lead molecules are bound by delta-aminolevulinic acid dehydratase enzyme (δ-ALAD), the second enzyme in the heme biosynthesis pathway. The binding of lead molecules inactivates δ-ALAD, and causes a rise in levels of its substrate, delta-aminolevulinic acid (δ-ALA) (Klaassen, 2006). Once in the brain, excess δ-ALAD disrupts the γ-aminobutyric acid (GABA)/glutamate system in several ways, creating potential for neuroexcitotoxic events and cell death (Brennan and Cantrill, 1979; Demasi et al., 1996; Emanuelli et al., 2003; Villayandre et al., 2005).

δ-ALA is an ω-amino acid with a five-carbon chain that structurally resembles γ-aminobutyric acid (GABA). Earlier reports suggested that δ-ALA was a GABA antagonist (Pierach and Edwards, 1978). More recent studies have shown that δ-ALA activates GABA_A autoreceptors, directly damages GABA_A receptor sites (Demasi et al., 1996) and stimulates glutamate release (Brennan and Cantrill, 1979). Excess δ-ALA also irreversibly inhibits glutamate uptake by astrocytes, by altering the glutamate transporter GLT-1 (Emanuelli et al., 2003). Moreover, the chronic presence of excess δ-ALA in the brain decreases NMDA receptor density (Villayandre et al., 2005). Questions have been raised regarding the amount of excess δ-ALA necessary to exert these disruptive and potentially neuroexcitotoxic effects (Lindberg et al., 1999). Results now suggest that extra-cellular concentrations of δ-ALA as low as 0.01 μM change sodium channel activation in isolated rat hippocampal CA1 neurons (Wang et al., 2005), thus indicating exquisite sensitivity of these neurons to very small increases in δ-ALA.

An endogenous mechanism that protects the brain from excess peptide-bound amino acids, such as δ-ALA, may also play a role in the neurotoxic potential of blood lead. Proton-coupled oligopeptide transporter (PEPT2, aka SLC15A2) is localized in two regions relevant to lead exposure. PEPT2 is highly expressed in the kidney where it is the principal protein responsible for reabsorption of di- and tripeptides (Shen et al., 1999); PEPT2 is also expressed at the blood-cerebrospinal fluid barrier, where it maintains homeostasis of neuropeptides and removes potential neurotoxins (Ocheltree et al., 2005). PEPT2 has been shown to lower δ-ALA in cerebrospinal fluid suggesting that PEPT2 may act as a secondary genetic modifier of neurotoxicity in cases of lead exposure (Hu et al., 2007). Thus for both ALAD and PEPT2, common functionally significant single-nucleotide polymorphisms have been identified, and either or both of these can impact the neurotoxic effects of blood lead.

δ-ALAD is encoded by two common variants of the gene (chromosome 9q34; Wetmur et al., 1991a) including ALAD1 and ALAD2 (Wetmur et al., 1991a). Estimated to occur in 15–20% of the Anglo, European and Asian populations studied (Benkman et al., 1983; Petrucci et al., 1982; Secchi et al., 1974) the ALAD2 polymorphism has a markedly higher affinity for lead (Battistuzzi et al., 1981). Adults exposed to moderate to high levels of lead, and who were heterozygous and homozygous for the ALAD2 polymorphism, had higher blood lead burden (Wetmur et al., 1991b; Schwartz et al., 1995; Fleming et al., 1998; Bergdahl et al., 1997; Ziensen et al., 1986). Fewer studies have examined ALAD2 in children. A recent study of 93 children living at various distances from a lead-contaminated area in Chile reported that the mean BLL of children with ALAD2 (14.2 μg/dL) was significantly higher than that of children with ALAD1 (9.5 μg/dL) (Pérez-Brago et al., 2004).

Researchers in China reported a similar finding. In 229 children, BLL in those with ALAD2 vs. ALAD1 differed significantly (9.7 μg/dL vs. 11.7 μg/dL) (Shen et al., 2001). The PEPT2 gene (chromosome 3q13.3; Ramamoorthy et al., 1995) also has two main variants – PEPT2*1 and PEPT2*2 – that differ significantly in their biochemical properties and functionality. Each is estimated to occur in approximately half of the typical population (Pinsonneault et al., 2004). Thus far, PEPT2 has been largely investigated as a potential drug transport mechanism (Shen et al., 2003). Enzyme kinetics studies have suggested that the binding potential of PEPT2*2 is substantially less than that of PEPT2*1 as indicated by their significantly different Km constants (233 ± 38 and 83 ± 16 μM, respectively) (Pinsonneault et al., 2004). Because PEPT2 clearly δ-ALA, it has been suggested that PEPT2 may be a secondary genetic modifier of neurotoxicity at choroid plexus (Hu et al., 2007).

In kidney, PEPT2 is expressed in the proximal tubule, which is also the primary distribution location of renal lead. Evidence has suggested that PEPT2 functions as the main mechanism for proximal tubular reabsorption of peptide-bound amino acids (Rubio-Alia et al., 2003). The metabolism of lead is complex and is not completely understood. Multiple secondary effects on blood lead level that occur as a result of lowered tubular reabsorption in children with the PEPT2*2 polymorphism are possible. For example, lead has been associated with increased production of over 100 different proteins (Witzmann et al., 1999). To the extent that lowered reabsorption of excess peptides may interact with lead clearance, the PEPT2*2 polymorphism might be associated with increased blood lead burden. Whether blood lead burden is associated with the PEPT2 polymorphism has yet not been examined in a human clinical study.

The only known means for treating children exposed to lead at low levels is source removal. Primary prevention is necessary to lower risk, particularly for minority children. If found to be associated with blood lead burden, ALAD2 and/or PEPT2*2 polymorphisms may prove to be novel biomarkers for identifying children at highest risk of exposure. Our goal in this study was to examine associations between ALAD2 and PEPT2*2 polymorphisms and blood lead burden in a sample of Mexican-American/Hispanic children at high risk of lead exposure.

2. Materials and methods

2.1. Participants

Permission to conduct these studies was obtained from the El Paso Independent School District Research Board and this project was approved by the Institutional Review Board of the University of Texas in El Paso. In El Paso, Texas, seven city zip codes have been designated “high risk” for lead exposure based on soil contamination tests conducted through the joint efforts of the U.S. Environmental Protection Agency, the Agency for Toxic Substances and Disease Registry, the Texas Department of Health, the Texas Commission on Environmental Quality (TCEQ) (ATSDR, 2004). All study forms and materials were available in Spanish and English versions. The elementary school from which these children were recruited was located in a zip code designated “high risk” for lead exposure by the EPA; the homes of 106/116 children (91.4%) were located in the same high-risk zip code, constituting 12% of same-age children in this zip code. The homes of the remaining 10 children were in one of 7 nearby zip codes, 5 of which were also designated “high risk” for lead exposure.

2.2. Procedures

2.2.1. Blood lead level testing

Blood lead levels were determined with the LeadCare II point-of-care device (ESA Magellan Biosciences, Chelmsford, MA). In clinical field trials conducted by ESA, the correlation of the LeadCare II device and graphite furnace atomic absorption spectroscopy (GFAAS) reference method was .979 overall, with the highest correlation (99.4%) attained for blood lead levels below 10 μg/dL. The mean coefficient of variation across four levels of blood lead was 0.072 (Feehey and Zink, 2006). The LeadCare II device was FDA-cleared as a quantitative blood lead evaluation device on the basis these data and subsequently classified as CLIA-waived. The LeadCare II device detects blood lead levels to 3.3 μg/dL. Blood lead levels below 3.3 μg/dL are read as “low.” For this...
study, children with blood lead levels ≥4.0 μg/dL were designated “exposed,” children with blood lead levels <3.2 μg/dL were designated “unexposed.” The pooled total standard deviation of blood lead levels obtained by the LeadCare manufacturer (ESA Magellan Biosciences) during precision testing was 0.64 μg/dL for blood lead levels below 10 μg/dL, thus children with screening blood lead levels between 3.3 and 3.9 were not included in either group. All testing was conducted during the school day. Child verbal assent was obtained immediately prior to testing.

Testers cleaned their hands with antiseptic foam soap and wore protective gloves, safety glasses and a lab coat during blood collection. Each child cleaned their hands for 10 s with antiseptic foam soap, followed by cleaning with chelating towelettes specially formulated for industry use to remove lead, and also nickel, silver, cadmium, and arsenic from the skin surface (D-Wipe®, Esca-Tech Inc., Milwaukee, WI). Saf-T-Pro™ 1.8 mm lancets were used for all draws and blood was collected in a 50-μL vial, mixed and tested within 3 h of the initial draw. Blood lead levels were recorded on each test vial, on each child’s testing form, and in the study database. All parents were provided with the results of their child’s blood lead level test. Throughout the study parents were provided with educational materials regarding lead exposure, verbally advised of the most common sources of lead exposure for children, and when indicated or requested, provided with referrals to local pediatrics.

2.2.2. Initial screening

A screening strategy was used to achieve equal representation of “exposed” and “unexposed” children, and to match exposed and unexposed children by sex and age. Letters from the school principal offering participation in the study were sent to all parents of currently enrolled children totaling 622 families; 222 parents (36%) completed informed consent, allowing initial blood lead level screening for 106 females and 116 males ranging in age from 4.1 to 12.5 years. Four children whose parents had signed consent refused to assent at the time of testing. Among the children tested, 57.7% had undetectable blood lead (128/222); 15.8% (35/222) of children had blood lead levels between 3.3 and 3.9; the remaining 27.5% of children (59/222) had blood lead levels ≥4.0 μg/dL (Table 1). A total of 116 children, 59 with screening blood lead levels ≥4.0 μg/dL and 57 age- and sex-matched controls with undetectable blood lead (2 children refused to assent at the time of testing), completed two additional blood lead level tests, genetic and neurocognitive testing (neurocognitive results are described in a separate manuscript, Sobin et al., unpublished data). For each child mean blood lead level was calculated from three time points. Controls were matched to within 9 months.

2.2.3. Genetic testing

Cheek cell collection, DNA extraction and single-nucleotide polymorphism detection were completed using proprietary technology developed by TrimGen Corporation, Sparks, MD. Cheek cells were collected using Easy-Swab™ foam collection swabs and DNA extraction was completed with BuccalQuick™ solution. Prior to each collection, children rinsed their mouths with water. Four samples were collected from each child, two from each cheek by brushing firmly up and down on the inside of the cheek, while rotating the swab. Each swab was marked with the child’s ID number and placed in the swab holder for drying. Swab heads were rinsed in extraction buffer, vortexed at high speed (10 s), incubated at 55 °C (60 s) and heated at 90 °C (180 s). Polymerase chain reaction amplification consisted of: 1 cycle 95 °C (5 s); 40 cycles of 95 °C (30 s), 53 °C (30 s) for ALAD2 or 56 °C (30 s) for PEPT2, 72 °C (30 s); 1 cycle 95 °C (5 s) using the following gene specific primers: PEPT2: F: 5′AGGAAAAATGCTTGTGTATGATC; R: 5′CGCAACTGCATAATGCCAG; ALAD: F: 5′GACGGTGGCTCGGGG; R: 5′TCCCTCTTAGCCCTCC

2.3. Data analysis

All variables were examined for outliers and distribution properties. Possible group differences in mean age and sex were examined using unpaired t-test and chi-square, respectively. Other clinical and demographic variables were compared using chi-square analysis. Blood lead levels were averaged across three time points. The LeadCare II device has a lowest detection limit of 3.3 μg/dL. For the group comparison of blood lead level, children with “low” (<3.2) blood lead were assigned the middle value between 0 and 3.2, that is, 1.6 μg/dL. For three children, blood lead level at one time point was missing, and their mean blood lead levels were averaged from two data points. The blood lead level distribution was log normal and Kruskal–Wallis (non-parametric) one-way ANOVA was used.

3. Results

3.1. Demographics

Data from 116 children were analyzed including 59 children with blood lead level ≥4.0 μg/dL, and 57 age- and sex-matched controls with no detectable blood lead at screening (2 controls declined participation). Parents of 97/116 children studied (83.6%) completed demographic information forms; 19 parents declined completion of the forms. The mean age of the sample was 8.1 (±1.9), and 48% were female (Table 2). Groups of children with and without detectable blood lead did not differ with regard to zip code of residence, or racial or ethnic composition. The parents of children in this sample were white, and of Mexican/Mexican-American/Hispanic/Latino descent. For additional comparisons of the demographic characteristics of children with and without detectable blood lead, multi-level variables were dichotomized, i.e., family income >20k, yes/no; and parent graduation from high school, yes/no. The exposed group differed with regard to family income and mothers’ educational achievement. As compared to children with undetectable blood lead, among children with average blood lead levels ≥4.0 μg/dL, family income was lower (df = 1, chi-square = 5.68, Fisher’s exact p = .031); and mother’s educational achievement was less (df = 1, chi-square = 13.4, Fisher’s exact p = .0004).

3.2. Blood lead levels

Blood lead levels from three time points were averaged for 113/116 children; for 3 children, average blood lead level was based on...
two time points. The 3-month average BLL of “exposed” and “unexposed” children differed significantly suggesting that group assignment based on initial blood lead level screening achieved meaningful group differentiation (mean diff = 2.04 μg/dL, df = 114, t = 5.47, p < .001). For children designated “exposed,” the 3-month BLL average was 4.9 μg/dL; for children designated “unexposed,” the 3-month BLL average was 2.8 μg/dL.

3.3. Polymorphisms of ALAD and PEPT2 and blood lead in Hispanic children

In this sample of Mexican-American/Hispanic children the frequency of the PEPT2*2 polymorphism was 46.6%; the frequency of the ALAD2 polymorphisms was 18.1% (Table 3). Whether either or a combination of these polymorphisms was associated with higher blood lead burden was examined. The distribution of blood lead levels was positively skewed and a non-parametric group
Comparison test for ≥3 groups (Kruskal–Wallis ANOVA) was used to examine differences in blood lead levels for children by polymorphism status (no polymorphism, heterozygous, or homozygous for the mutation). The blood lead levels of children homozygous for the PEPT2*2 (n = 8) differed significantly from those of children heterozygous for, or without, the polymorphism (H = 5.98; df = 2; p = .050). The geometric mean values for these groups were: homozygous = 5.48 μg/dL; heterozygous = 3.78 μg/dL; no polymorphism = 4.08 μg/dL (Fig. 1). With regard to ALAD2, one child was homozygous for the polymorphism and 20 children were heterozygous for the polymorphism. The blood lead level of the child homozygous for the polymorphism was 4.7 μg/dL. For the statistical analysis of ALAD2, this case was grouped with heterozygous ALAD2 cases. Blood lead levels in children with the ALAD2 polymorphism did not differ significantly (U = 847.5; p = .229). Their geometric mean BLL values were: homozygous = 4.7 μg/dL; heterozygous = 3.8 μg/dL; no polymorphism = 4.0 μg/dL. The possible combined effects of these polymorphisms on blood lead burden were also examined. Due to restricted numbers of children in some cells (Table 4) a statistical analysis of differences could not be conducted. The numbers are presented for descriptive purposes and require analysis in future studies with larger numbers of children carrying a full complement of genetic combinations.

### 4. Discussion

#### 4.1. Low-level lead exposure in minority children

Efforts to reduce the frequency of blood lead levels above 10 μg/dL in young children have been remarkably successful in recent decades. Now is an opportune time to direct attention to the risks of blood lead levels in children below this current threshold for toxicity. Over 40 clinical studies have shown an association between subclinical blood lead and altered cognitive and behavioral functions (Workgroup, 2004; Davis et al., 2004; Jusko et al., 2008). It is well established that minority children are at grossly increased risk of lead exposure (Bernard and McGeethin, 2003) and the large number of facilities throughout the U.S. that annually emit lead into the air and soil should raise concern for vulnerable child populations. Hispanic children represent the fastest growing ethnic population in the United States. Between 1990 and 2006, the number of Hispanic children in U.S. public schools doubled, representing 60% of the total growth of public school populations during this time period (Fry and Gonzales, 2008). The prevalence of lead toxicity among toddlers in the city of El Paso is reported to be close to the gross national average (2%) (ATSDR, 2004). Similar to many cities with a high proportion of minority children however, a multiplicity of factors greatly increases the risk of chronic subclinical lead exposure. Lead-based paint in unrenovated housing is still common in older and in economically depressed parts of the city. Parents whose jobs require them to work with lead solder and car batteries, in factories, metalwork shops, or automotive repair industries, can carry lead into the home on their clothes and skin. For some children, traditional medicines, cures, and random consumer goods such as certain candies, candy wrappers, jewelry, cookware and pottery, pose a significant threat. Moreover, from 1899 to 1999 the American Smelting and Refining Company (ASARCO) operating next to downtown El Paso, emitted hundreds of tons of lead, contaminating the soil in zip codes resided in by children in this study (Ketter, 2006).

Children sampled in this study resided in neighborhoods wherein approximately 90% of residences were built before 1978, the year in which the federal anti-lead paint laws were enacted. Lower socio-economic status and its associated risk factors, including compromised nutrition and lowered quality of physical living condition (MMWR, 2000) can also increase the risk of blood lead burden. The published mean of median household incomes in the zip codes from which children in this study were selected was $21,240, with 33.7% of households reported to be living below the poverty level (City, 2008). The annual reported income of families in this sample closely approximated these figures (Table 1). Group differences in parent education and family income, between children with and without detectable blood lead level, were consistent with past reports of risk factors for lead exposure. Furthermore, in this sample, risk of low blood lead burden did not appear to decrease from ages 4.1 to 12.5 years.

It has been estimated that 23% of minority children ages 1–5 had blood lead levels between 5 and 10 μg/dL (Bernard and McGeethin, 2003). While this study did not use an epidemiologic approach, the identification of 27% of children with blood lead levels above 4.0 μg/dL suggested that exposure to subclinical levels of lead is occurring among a large percentage of school-age minority children living in areas at high risk for lead exposure. This requires further examination using a probability sampling approach.

#### 4.2. Genetic biomarkers of neurotoxic risk in low-level lead exposure

Identifying a biomarker of increased risk among high-risk children could provide a tool for primary prevention, and may suggest mechanisms to target for intervention. Previously, large inter-ethnic differences in the frequencies of PEPT2 variants have been reported (Liu et al., 2009). Our findings suggested that the PEPT2*2 polymorphism is common among children of Mexican-American/Hispanic descent, and closely approximates the frequency of the PEPT2 polymorphisms in North American Caucasian populations, previously estimated to be approximately 50% (Pinsonneault et al., 2004). A large proportion of school-age Hispanic children carry this common genetic polymorphism that may have implications for the long-term effects of subclinical lead exposure. Among children homozygous for the PEPT2*2 polymorphism, blood lead burden was increased. Results from previous animal studies have suggested that PEPT2 may be a secondary genetic modifier in cases of lead poisoning (Hu et al., 2007). Our results suggest that PEPT2 may also be a secondary genetic modifier in cases of lowest level lead exposure. The neuroprotective effects of PEPT2 have only recently been described and the relationship between diminished δ-ALA clearing and blood lead burden, particularly in cases of lower level exposures, is not yet understood. Nonetheless, in future studies of subclinical lead
exposure, it will be important to assess and control for children's PEPT2 status, and to include this genotype in animal models of lead exposure.

Previous studies have suggested that children heterozygous and homozygous for the ALAD2 polymorphism had higher blood lead burden (Pérez-Bravo et al., 2004; Shen et al., 2001). The frequencies of the ALAD2 polymorphism in this sample closely approximated those previously reported in Anglo, European and Asian samples (see above). However, no association between ALAD2 and subclinical blood lead burden was found in this study. One explanation for this may be the relatively low number of children homozygous vs. heterozygous for the polymorphism. A second explanation may be that the impact of ALAD2 polymorphism is highly variable in cases of lowest level lead exposure. This awaits further study.

4.3. Limitations

The LeadCare II analyzer was used for this study. This device is cost- and time-efficient, allowing for large-scale screening in public school settings. Its lower limit of 3.2 μg/dL however is relatively arbitrary. Additional studies of these polymorphisms using methods with a lower detection limit are warranted. Moreover, a replication of these findings that includes a greater number of children homozygous for the PEPT2*2 polymorphism is needed. This study was conducted in one elementary school located in one of seven El Paso zip codes designated “high risk” for lead exposure by the EPA. Samples from additional high-risk zip codes are required to increase the representativeness of these studies, and to replicate and extend these findings. Samples from non-high-risk zip code neighborhoods are also needed for comparison studies.

4.4. Conclusions

Among a sample of Mexican-American/Hispanic children, the rates of the ALAD2 PEPT2*2 polymorphisms were roughly equivalent to those previously reported in Anglo, European and Asian populations. At lead exposures below the current threshold of toxicity, the PEPT2*2 polymorphism is associated with higher blood lead burden and may provide a biomarker of neurotoxic risk in cases of lowest level lead exposure. Subclinical lead exposure has long been associated with diminished cognitive function and should be of major concern to child health care professionals, researchers and educators. National efforts to eradicate child lead poisoning (BLL > 10 μg/dL) have been extremely successful; an equal investment in the primary prevention of subclinical blood lead levels is warranted, in order to protect the mental health and development of rapidly increasing numbers of school-age minority children living in high-risk areas of the United States.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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