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Genetic variation in metallothionein and metal-regulatory transcription factor 1 in relation to urinary cadmium, copper, and zinc

Scott V. Adams [a,*], Brian Barrick [b], Emily P. Christopher [a], Martin M. Shafer [c], Karen W. Makar [d], Xiaoling Song [a,d], Johanna W. Lampe [a], Hugo Vilchis [e], April Ulery [b], Polly A. Newcomb [a]

[a] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, Seattle, WA 98109, USA
[b] Department of Plant and Environmental Sciences, New Mexico State University, Box 30003 MSC 3Q, Las Cruces, NM 88003, USA
[c] Environmental Chemistry and Technology, Wisconsin State Laboratory of Hygiene, University of Wisconsin, 2601 Agriculture Dr., Madison, WI 53718, USA
[d] Public Health Science Biomarker Laboratory, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, Seattle, WA 98109, USA
[e] Border Epidemiology and Environmental Health Center, New Mexico State University, Box 30001 MSC 3BEC, Las Cruces, NM 88003, USA

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ABSTRACT

Background: Metallothionein (MT) proteins play critical roles in the physiological handling of both essential (Cu and Zn) and toxic (Cd) metals. MT expression is regulated by metal-regulatory transcription factor 1 (MTF1). Hence, genetic variation in the MT gene family and MTF1 might influence excretion of these metals.
Methods: 321 women were recruited in Seattle, WA and Las Cruces, NM and provided demographic information, urine samples for measurement of metal concentrations by mass spectrometry and creatinine, and blood or saliva for extraction of DNA. Forty-one single nucleotide polymorphisms (SNPs) within the MTF1 gene region and the region of chromosome 16 encoding the MT gene family were selected for genotyping in addition to an ancestry informative marker panel. Linear regression was used to estimate the association of SNPs with urinary Cd, Cu, and Zn, adjusted for age, urinary creatinine, smoking history, study site, and ancestry.
Results: Minor alleles of rs28366003 and rs10636 near the MT2A gene were associated with lower urinary Cd, Cu, and Zn. Minor alleles of rs8044719 and rs1599823, near MT1A and MT1B, were associated with lower urinary Cd and Zn, respectively. Minor alleles of rs4653329 in MTF1 were associated with lower urinary Cd.
Conclusions: These results suggest that genetic variation in the MT gene region and MTF1 influences urinary Cd, Cu, and Zn excretion.

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1. Introduction

Metallothioneins (MTs) are a family of evolutionarily conserved, small cysteine-rich proteins that bind transition metal ions, including with highest affinity zinc (Zn), copper (Cu), and cadmium (Cd) (Bremner and Beattie, 1990; Hamer, 1986; Isani and Carpene, 2014; Vasak and Meloni, 2011). MTs are critical to homeostasis of the essential micronutrients Zn and Cu, and for detoxification of the toxic metal Cd, and also likely serve as reactive oxygen species scavengers (Babula et al., 2012). However, uncertainty over the many putative cellular functions of MTs remains (Isani and Carpene, 2014; Palmiter, 1998). The handling of metal ions by MT has been suggestively implicated in a variety of diseases including Alzheimer's disease (Carrasco et al., 2006; Luo et al., 2013), cancer risk and progression (Goulding et al., 1995; Kelley et al., 1988; Kim et al., 2011), and renal and liver toxicity due to heavy metals (Klaassen and Liu, 1997).

* Corresponding author at: Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, M4-B402, Seattle, WA 98109, USA.
E-mail address: sadams@fhcrc.org (S.V. Adams).

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In addition to critical roles in handling metals, MTs are transcriptionally regulated in response to metal ions. A key protein in this process is metal-regulatory factor 1 (MTF1), which binds metal responsive elements located upstream of MT genes in the presence of heavy metals (Palmiter, 1994). This step may be the critical pathway to the induction of MT in response to metals (Jiang et al., 2003), and thus genetic variation in MTF1 may modulate expression of MT and thereby influence biological management of metals (Sims et al., 2012).

Earlier studies of genetic variation in MT genes have generally taken a candidate-gene approach in which a few single-nucleotide polymorphisms (SNPs) are analyzed. Nonetheless, these studies have identified suggestive associations with risk of several cancers (Forma et al., 2012; Krzeslak et al., 2012; Starska et al., 2014; Zavras et al., 2010), diabetes (Giacconi et al., 2005; Yang et al., 2008), and other diseases (Chen et al., 2010; Chen et al., 2012; Giacconi et al., 2007; Hayashi et al., 2006) as well as levels of metals in biological matrices such as blood, urine, and kidney tissue (Chen et al., 2012; Kayaalti et al., 2010; Kayaalti et al., 2011; Lei et al., 2012; Raudenska et al., 2014). However, candidate SNP studies such as these—in which a very small number of SNPs are analyzed—may miss other important genetic variation, cannot assess whether the identified associations may be due to additional

SNPs in disequilibrium with the candidate SNPs, and require further validation in additional populations. Therefore, to shed further light on the relevance of genetic variation in MT and MTF1 to physiological control of metals, we were motivated to take a more systematic approach to exploring the associations of MT and MTF1 SNPs with urinary levels of Cd, Cu, and Zn.

2. Methods

2.1. Study populations

For this study, data were pooled from participants recruited for two earlier studies: the Equol, Breast and Bone (EBB) study in Seattle, Washington (Atkinson et al., 2008a) and the New Mexico Metals (NMM) study in the Doña Ana County, New Mexico region (previously unpublished). Data were pooled for three reasons: (1) to increase sample size; (2) to increase the genetic variation included in the study; and (3) increase the ranges of urinary cadmium, copper, and zinc in the study population. All three of these factors would increase statistical power to observe associations.

2.1.1. EBB. The recruitment, exclusion criteria, and clinical protocols of the EBB study have been detailed elsewhere (Atkinson et al., 2008a; Atkinson et al., 2009). Briefly, premenopausal women aged 40–45 years were recruited from a mammographic screening program within Group Health (GH), an integrated healthcare system in Washington State. Based on self-report, peri- and postmenopausal women, women with a history of breast cancer, women with certain digestive conditions and women using antibiotics were also excluded. Study procedures were approved by the Fred Hutchinson Cancer Research Center (FHCRC) and GH Institutional Review Boards.

2.1.2. NMM. Women and men age 40–85 were recruited by *promotoras* (community health workers) employed by the *La Clinica de Familia* primary care clinic network in southern New Mexico. *La Clinica de Familia* is a non-profit organization serving approximately 6500 low income and rural residents of the Doña Ana County, NM region. Participants were recruited in two time periods, 2011 and 2012. All participants provided written informed consent. Interviews were conducted in either English or Spanish.

2.2. Data collection

2.2.1. Questionnaires. Participants in the EBB and NMM studies completed differing questionnaires that each included demographics and smoking history as well as other dietary, lifestyle, and health topics. Height and weight were measured in the clinic for EBB study articipants and self-reported for NMM study participants. EBB study participants completed a self-administered questionnaire; NMM questionnaires were interviewer-assisted.

2.2.2. Urinary metals. Participants in both studies provided spot urine samples collected in polyethylene collection cups. Samples were refrigerated, aliquoted, and stored at −70 °C until shipment for trace metals and creatinine analysis.

Urine samples were shipped frozen to the Trace Element Research Laboratory at the Wisconsin State Laboratory of Hygiene (Madison, WI) for assay of a suite of 30 elements, including Cd, Cu, and Zn, quantified using magnetic-sector (high-resolution) inductively-coupled plasma mass spectrometry (SF-ICP-MS). A Finnigan, Element 2, magnetic sector ICP-MS, interfaced with an ESI FAST (SC-E2-DXS) high efficiency, low-flow nebulizer/autosampler, was employed. The complete analytical system was located within a trace metal clean room. This approach enabled accurate and precise quantification of low levels of elements in complex urine matrices. The signal-to-noise of SF-ICPMS is superior to that of quadrupole ICP-MS, and when operated in medium or high resolution modes, spectral interferences that compromise quantification of many elements in urine by traditional quadrupole ICP-MS, are eliminated. The formation of molybdenum oxide (MoO) is monitored throughout the analytical sequence, and where appropriate, a run position empirical correction is applied to the cadmium data. MoO formation was also evaluated with molybdenum stable isotope spikes in selected participant samples. Urine samples were diluted 1 + 5:6 and 1 + 9 with 2% (*v*/*v*) high purity 16 M nitric acid (containing three internal standards) for analysis. A minimum of three replicate 180-second analyses were performed on each sample after a 60-second uptake and stabilization period. The ESI sample with a long rinse with 2% high purity nitric acid + 0.01% Triton between samples virtually eliminated carry-over. The typical SF-ICP-MS batch included 20 participant samples, 2 sample matrix spikes, 2 blank spikes, 3 certified reference materials (CSRMs, including NIST 2670a, UTAK, and Seronorm), 3 matrix blanks, 2 method blanks, 2 sample duplicates, and a set of check blanks and calibration verification checks run at frequent intervals during the batch sequence.

Urine creatinine was measured at the Fred Hutchinson Cancer Research Center Public Health Sciences Biomarker Laboratory with a Roche Cobas Mira Plus Chemistry Analyzer using creatinine reagent set (cat no C7539, Pointe Scientific, Inc., Canton, MI), following manufacturer's instructions. The Chemistry Analyzer was calibrated with the Pointe Scientific creatinine standard (cat no. C7513-STD). Samples were run in duplicates; median duplicate coefficient of variation (CV) was 1.7%. Each batch of 20 participant samples were bracketed by both a low and a high quality control (QC) sample (Pointe Scientific Human urine control set, cat no. P7582-CTL).

2.2.3. Single nucleotide polymorphism (SNP) selection. Several approaches were used to select SNPs. First, SNPs described in published reports related to cadmium were included (rs28366003, rs10636, and rs11076161)(Chen et al., 2012; Kayaalti et al., 2010; Kayaalti et al., 2011; Lei et al., 2012). Next we used the Genome Variation Server (GVS v. 7, dbSNP build 137; May 2012, current version: http://gvs.gs.washington.edu/GVS138/index.jsp) (Carlson et al., 2004) to identify tag SNPs, with bin correlation set to $r^2 \geq 0.50$, throughout the MT gene family and MTF1 regions and retaining SNPs with minor allele frequency (MAF) ≥15% within the HapMap CEU and MEX populations. We selected SNPs within ~2.5 kbp upstream of MT4A and ~4.2 kbp downstream of MT1X, i.e., ±3 kbp of the ~124 kbp region of chromosome 16 encoding the metallothionein (MT) gene family. MTF1 SNPs were selected from the beginning of the 5′ UTR to the end of the 3′ UTR (~50 kbp total length). A preliminary list of SNPs was optimized for Illumina Golden Gate sequencing technology, resulting in substitution of tag SNPs within the same "bin" to optimize the oligo pool assay (OPA) design score. In this process rs11076160 was substituted for rs11076161 ($r^2 = 1.0$ and 0.96 in HapMap-CEU and MEX, respectively). A final list of 41 candidate SNPs comprising 35 tag bins ($r^2 \geq 0.5$) in MT genes and 5 SNPs comprising 5 bins in the MTF1 gene was generated for genotyping. In addition, participant genotypes of 24 SNPs designed as an ancestry informative marker (AIM) panel suitable for populations in the Americas (Kosoy et al., 2009) were assayed.

2.2.4. DNA preparation and genotyping. For EBB samples, DNA was extracted from the buffy coat fraction of a study blood sample using a Qiagen blood kit as described (Atkinson et al., 2008b; Yong et al., 2010). For NMM samples, saliva collected with OraGene OGR-500 kits (DNA Genotek Inc., Ontario, Canada) and DNA extracted in the FHCRC Specimen Processing Laboratory. Previous studies have demonstrated the concordance of genotypes obtained with DNA from blood and saliva (Abraham et al., 2012).

DNA was genotyped using Illumina's GoldenGate Genotyping assay on the VeraCode Platform (Illumina, San Diego, CA) (Shen et al., 2005) following manufacturer recommendation (VeraCode Assay Guide 11,312,819 rev A1). In brief, 250 ng of genomic DNA was aliquoted

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