

**Supplementary material**

**Cadmium Concentrations in Human Blood and Urine are Associated with  
Polymorphisms in Zinc Transporter Genes**

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**Table 1 (supplementary material).** Polymorphisms of the *SLC39A14* and *SLC39A8* genes that were successfully genotyped. Quality requirements: HWE<sup>a</sup> and 90% of samples easily recognized in the mass spectrometry analysis

Gene	rs nr <sup>b</sup>	Polymorphism type <sup>c</sup>	Allele frequencies Argentina	QC (%) <sup>a</sup>	Allele frequencies Bangladesh	QC (%) <sup>a</sup>
<i>SLC39A14</i>	rs870215	Intron A>G	10/90	97	16/84	96
	rs896377	Intron C>G	4/96	97	22/78	97
	rs896378	P33L T>C	48/52	98	43/57	99
	rs1051638	3' UTR G>A	44/56	98	45/55	98
	rs2293144	L65L A>G	40/60	98	37/63	99
	rs4872479	Intron T>G	7/93	97	7/93	96
	rs7818776	Intron A>C	55/45	96	39/61	95
	rs11783730	Intron T>C	48/52	97	33/67	99
	rs11989798	Intron C>A	3/97	96	13/87	95
	rs13259873	Intron T>C	51/49	98	47/53	99
	<i>SLC39A8</i>	rs9705	3' UTR A>G	60/40	98	23/77
rs233804		Intron A>C	8/92	97	36/64	100
rs233818		Intron T>C	63/37	95	27/73	97 (*)
rs233825		Intron G>A	12/88	97	36/64	98 (*)
rs233827		Intron A>G	15/85	96	53/47	98
rs390878		Intron T>C	60/40	96	28/72	98
rs971752		Intron G>A	16/84	97	26/74	97
rs998719		Intron C>T	11/89	96	22/78	98
rs1462947		Intron A>G	-	84(**)	32/68	92
rs1545744		Intron T>A	16/84	100	25/75	99
rs2165265		Intron G>T	23/77	93 (*)	20/80	96
rs4699011		Intron T>C	16/84	98	26/74	99
rs6822371		Intron T>G	19/81	97	30/70	98
rs6829701		Intron A>G	10/90	97	31/69	99
rs6848517		Intron C>G	70/30	97	38/62	100
rs7436937		Intron T>G	70/30	97	37/63	95
rs7655493		Intron C>T	27/73	92	37/63	94
rs7664683		Intron T>C	2/98	97	23/77	99
rs7681239		Intron C>T	3/97	96	18/82	93
rs10014145		Intron G>A	13/87	98	36/64	97
rs11941736		Intron C>G	10/90	98	30/70	98
rs13103835		Intron G>A	19/81	97	30/70	98
rs13107325		A391T G>A	1/99	98	1/99	99
rs17032363		3' UTR G>A	0/100	97	1/99	94
rs17226148		Intron G>A	7/93	96	13/87	98
rs17823966		H347H C>T	0/100	100	8/92	99

<sup>a</sup> If there was Hardy-Weinberg disequilibrium in both populations, the polymorphism was excluded. Polymorphisms that demonstrated disequilibrium in one of the populations are marked with (\*). A polymorphism was excluded in one population for quality reasons (\*\*).

<sup>b</sup> Rs numbers from NCBI SNP Database (website: <http://www.ncbi.nlm.nih.gov/SNP>).

<sup>c</sup> When applicable, amino acid position/gene region is denoted.

**Table 2 (supplementary material).** Modification by SNPs of putative transcription factor binding sites.

Gene SNP	Allele	Effect	Site affected Family/Factor	Description
<b><i>SLC39A14</i></b>				
rs4872479	G -> T	lost	CEBP/CEBP02	CCAAT/enhancer binding protein
rs870215	G -> A	new	HOXH/MEIS1A_HOXA	Meis homeobox 1
<b><i>SLC39A8</i></b>				
rs10014145	A -> G	lost	NKXH/NKX31	NK3 homeobox 1, NKX-3 ALPHA
rs233804	C -> A	new	TALE/MRG1	Meis homeobox 2 (Meis2)

**Table 3 (supplementary material).** Expression probes for *SLC39A8* and *SLC39A14*.

Gene	Probe No	Sequence	Median <sup>a</sup> (min-max)
<i>SLC39A8</i>	ILMN_1695316	GGTTGCACCCCTCACAAATGGCAGAACAGTATGTAAAGCTGGTAACACCT <sup>b</sup>	155 (110-210)
	ILMN_2233539	GTGTGATCGAGAGCCATTCAGAAAAGACTTCCTTTGTGTTCAGCCTATAC <sup>b</sup>	163 (97-280)
<i>SLC39A14</i>	ILMN_1764629	TGTCACGTGCAGGAACAGTGAGGCAGGGACAGGGGTTCTGCTCCTTCTCA <sup>c</sup>	102 (83-120)

<sup>a</sup> Expression in relative fluorescence units.

<sup>b</sup> Located on exon 8b covering transcripts 1, 2 and 4 but not 3 ([www.ncbi.nih.gov/nucleotide](http://www.ncbi.nih.gov/nucleotide)).

<sup>c</sup> Located on exon 11 covering transcripts 1, 2 and 3 ([www.ncbi.nih.gov/nucleotide](http://www.ncbi.nih.gov/nucleotide)).

**Table 4 (supplementary material).** Spearman's correlation coefficients ( $r_s$ ) between cadmium levels in erythrocytes (Ery-Cd), blood (B-Cd) and urine (U-Cd), plasma zinc (P-Zn), ferritin in plasma, age and parity in the Bangladeshi and Argentinean Andes populations.

		Parity		Ery-Cd <sup>a</sup>		B-Cd		U-Cd		P-Zn		Plasma Ferritin	
		Andes	Bangladesh	Andes <sup>b</sup>	Bangladesh	Andes <sup>b</sup>	Bangladesh	Andes <sup>b</sup>	Bangladesh	Andes	Bangladesh	Andes <sup>b</sup>	Bangladesh
Age	$r_s$	0.63	0.76	0.33	0.21	0.40	—	0.42	0.28	0.24	-0.08	0.50	0.03
	P	<0.001	<0.001	<0.001	<0.001	<0.001	—	<0.001	<0.001	0.002	0.1	<0.001	0.6
	N	167	403	172	400	172	—	172	340	157	399	166	399
Parity	$r_s$			0.33	0.19	0.40	—	0.41	0.31	0.25	-0.08	0.30	0.03
	P			<0.001	<0.001	<0.001	—	<0.001	<0.001	0.002	0.1	<0.001	0.6
	N			167	400	167	—	167	340	154	399	161	399
Ery-Cd	$r_s$					0.97	—	0.42	0.47	0.03	-0.02	-0.09	-0.18
	P					<0.001	—	<0.001	<0.001	0.7	0.6	0.3	<0.001
	N					172	—	172	337	157	396	166	396
B-Cd	$r_s$							0.45	—	0.11	—	0.03	—
	P							<0.001	—	0.2	—	0.7	—
	N							172	—	157	—	166	—
U-Cd	$r_s$									0.20	-0.07	0.21	-0.10
	P									0.01	0.2	0.008	0.06
	N									157	336	166	336
P-Zn	$r_s$											0.18	0.06
	P											0.02	0.3
	N											156	397

<sup>a</sup> Cd in erythrocytes calculated in Argentinean Andes, measured in Bangladesh.

<sup>b</sup> Numbers for Argentinean Andes quoted from EHP, 121 (4) 2013, 467-472.

— Not measured.

**Table 5 (supplementary material).** Gene expression (relative units) as a function of genotype measured in a subset of the Andean population (P-values of Kruskal-Wallis test).

Gene	SNP	Genotype	Median	Range	N	P-value	
<i>SLC39A14</i>							
rs4872479		GG	101	83 - 120	61	0.7	
		GT	100	92 - 110	10		
rs870215		GG	101	83 - 120	58	0.8	
		AG/AA	100	92 - 110	13		
<i>SLC39A8</i>							
rs10014145		AA <sup>a</sup>	155	110 - 210	61	1.0	
		AG/GG	158	120 - 180	11		
		AA <sup>b</sup>	155	97 - 280	61		0.2
		AG/GG	145	110 - 230	11		
rs233804		CC <sup>a</sup>	<b>157</b>	<b>110 - 210</b>	<b>65</b>	<b>0.049</b>	
		CA/AA	<b>140</b>	<b>120 - 160</b>	<b>7</b>		
		CC <sup>b</sup>	155	97 - 280	65		0.3
		CA/AA	145	110 - 180	7		

<sup>a</sup> Probe ILMN\_1695316.

<sup>b</sup> Probe ILMN\_2233539.

**Table 6 (supplementary material).** Spearman's rho correlation between expression of *SLC39A8* and metal biomarkers in a subset of the Andean population, both for total expression (A) and per genotype of rs10014145 and rs233804 (B).

A. Total expression					
		B-Cd	U-Cd	P-Zn	ferritin
SLC39A8 <sup>a</sup>	r <sub>S</sub>	-0.02	-0.07	-0.09	-0.06
	P	0.9	0.6	0.5	0.6
	N	72	72	64	70
SLC39A8 <sup>b</sup>	r <sub>S</sub>	0.08	0.00	0.02	-0.22
	P	0.5	0.9	0.9	0.07
	N	72	72	64	70
B Expression by SNP/Genotype					
rs10014145					
AA <sup>a</sup>	r <sub>S</sub>	0.01	-0.09	-0.13	-0.01
	P	0.9	0.5	0.3	0.9
	N	61	61	54	60
AG/GG <sup>a</sup>	r <sub>S</sub>	-0.19	0.04	0.05	-0.26
	P	0.6	0.9	0.9	0.5
	N	11	11	10	10
AA <sup>b</sup>	r <sub>S</sub>	0.10	-0.01	-0.01	-0.21
	P	0.5	0.9	0.9	0.1
	N	61	61	54	60
AG/GG <sup>b</sup>	r <sub>S</sub>	0.02	0.31	0.08	-0.15
	P	0.9	0.4	0.8	0.7
	N	11	11	10	10
rs233804					
CC <sup>a</sup>	r <sub>S</sub>	0.05	-0.10	-0.12	-0.08
	P	0.7	0.4	0.4	0.5
	N	65	65	57	63
CA/AA <sup>a</sup>	r <sub>S</sub>	0.14	0.00	0.40	0.11
	P	0.8	1.0	0.4	0.8
	N	7	7	7	7
CC <sup>b</sup>	r <sub>S</sub>	0.18	-0.01	0.01	-0.22
	P	0.1	0.9	0.9	0.08
	N	65	65	57	63
CA/AA <sup>b</sup>	r <sub>S</sub>	-0.43	-0.18	0.05	-0.43
	P	0.3	0.7	0.9	0.3
	N	7	7	7	7

<sup>a</sup> Probe ILMN\_1695316.

<sup>b</sup> Probe ILMN\_2233539.