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Supplemental Material

N-6-Adenine-Specific DNA Methyltransferase 1 (*N6AMT1*) Polymorphisms and Arsenic Methylation in Andean Women

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Supplemental Material Table S1. Characteristics of study participants from San Antonio de los Cobres and surrounding villages.

	San Antonio de los Cobres (N=154)		Other villages (N=34)		
Characteristics	Mean	P 5th-95th	Mean	P 5th-95th	p-value ANOVA
Age	37	18-64	37	21-63	0.95
Years of Residence	26	5.0-52	25	0.0-53	0.69
BMI	26	19-35	25	18-39	0.22
U-As (µg/L)	277	116-543	59	18-117	<0.001
%iAs	13	4.7-23	13	4.9-25	0.59
%DMA	79	66-89	79	65-90	0.80
%MMA	8,8	4.3-15	7,9	3.3-18	0.15

Supplemental Material Table S2. Comparison between study participants recruited 2008 and 2011.

	San Antonio de los Cobres					Surrounding villages				
	2008 (N=137)		2011 (N=17)			2008 (N=17)		2011 (N=17)		
Characteristics	Mean	P 5th-95th	Mean	P 5th-95th	p-value ANOVA	Mean	P 5th-95th	Mean	P 5th-95th	p-value ANOVA
Age	38	18-64	31	15-50	0.04	35	20-76	40	22-63	0.36
Years of residence	27	5.0-58	22	4.0-50	0.14	21	0.0-53	30	0.5-56	0.12
BMI	26	19-35	26	20-34	0.88	23	17-39	26	19-39	0.06
U-As (μg/L)	284	123-543	215	20-604	0.07	56	14-117	63	22-147	0.55
%iAs	13	4.9-23	10	2.4-23	0.09	15	4.9-29	11	3.7-23	0.11
%DMA	78	66-88	81	64-93	0.14	77	64-90	81	65-92	0.10
%MMA	8.8	4.3-15	8.7	3.7-15	0.89	8.0	3.1-18	7.7	3.3-19	0.81

Supplemental Material Table S3. Multivariable regression analyses[a] for arsenic metabolites and *AS3MT* haplotype.

Metabolite	Statistical Model	*AS3MT* Haplotype[b]	Mean (95% CI)[c]	β (95% CI)	p
iAs	Model 1	2 copies	11.4 (10.2, 12.6)		
		1 copy	13.5 (12.1, 14.8)	2.1 (0.27, 3.9)	0.025
		0 copies	15.3 (12.8, 17.8)	3.4 (1.1, 6.7)	0.0066
	Model 2	2 copies	11.4 (10.2, 12.6)		
		1 copy	13.5 (12.1, 14.8)	2.1 (0.27, 3.9)	0.025
		0 copies	15.3 (12.8, 17.8)	3.9 (1.1, 6.7)	0.0068
	Model 3	2 copies	11.4 (10.1, 12.6)		
		1 copy	13.5 (12.2, 14.8)	2.2 (0.33, 4.0)	0.021
		0 copies	15.3 (12.9, 18.0)	4.1 (1.3, 7.0)	0.0047
	Model 4	2 copies	11.4 (10.1, 12.6)		
		1 copy	13.5 (12.2, 14.8)	2.2 (0.35, 4.0)	0.020
		0 copies	15.3 (12.9, 18.0)	4.1 (1.3, 7.0)	0.0043
	Model 5	2 copies	11.4 (10.1, 12.6)		
		1 copy	13.5 (12.2, 14.9)	2.2 (0.33, 4.0)	0.021
		0 copies	15.3 (12.9, 18.1)	4.2 (1.3, 7.1)	0.0051
	Model 6	2 copies	11.4 (10.1, 12.6)		
		1 copy	13.5 (12.1, 14.9)	2.1 (0.31, 4.0)	0.022
		0 copies	15.3 (12.9, 17.9)	4.0 (1.2, 6.9)	0.0054
	Model 7	2 copies	11.4 (10.1, 12.5)		
		1 copy	13.5 (12.2, 14.9)	2.2 (0.41, 4.1)	0.017
		0 copies	15.3 (13.0, 18.1)	4.2 (1.4, 7.1)	0.0040
	Model 8	2 copies	11.4 (10.1, 12.6)		
		1 copy	13.5 (12.2, 14.8)	2.3 (0.35, 4.0)	0.020
		0 copies	15.3 (12.9, 18.0)	4.1 (1.3, 7.0)	0.004
MMA	Model 1	2 copies	7.4 (6.7, 8.0)		
		1 copy	9.4 (8.7, 10.1)	2.0 (1.0, 2.9)	0.000062
		0 copies	10.7 (9.3, 12.0)	3.3 (1.8, 4.7)	0.000020
	Model 2	2 copies	7.4 (6.8, 8.1)		
		1 copy	9.4 (8.6, 10.0)	1.9 (0.97, 2.9)	0.000095
		0 copies	10.7 (9.3, 11.9)	3.2 (1.7, 4.6)	0.000033
	Model 3	2 copies	7.4 (6.9, 8.1)		
		1 copy	9.4 (8.6, 10.0)	1.8 (0.88, 2.8)	0.00017
		0 copies	10.7 (9.0, 11.7)	2.8 (1.4, 4.3)	0.00016
	Model 4	2 copies	7.4 (6.9, 8.1)		
		1 copy	9.4 (8.6, 10.0)	1.8 (0.89, 2.8)	0.00016
		0 copies	10.7 (9.1, 11.7)	2.9 (1.4, 4.4)	0.00012
	Model 5	2 copies	7.4 (6.9, 8.1)		
		1 copy	9.4 (8.6, 10.0)	1.8 (0.85, 2.7)	0.00025
		0 copies	10.7 (9.1, 11.8)	2.9 (1.4, 4.4)	0.00016
	Model 6	2 copies	7.4 (6.8, 8.1)		
		1 copy	9.4 (8.6, 10.0)	1.9 (0.92, 2.8)	0.00015
		0 copies	10.7 (9.2, 11.8)	3.1 (1.6, 4.5)	0.000061
	Model 7	2 copies	7.4 (6.9, 8.2)		
		1 copy	9.4 (8.6, 10.0)	1.7 (0.80, 2.7)	0.00033
		0 copies	10.7 (9.0, 11.6)	2.8 (1.3, 4.2)	0.00029
	Model 8	2 copies	7.4 (6.9, 8.1)		
		1 copy	9.4 (8.6, 10.0)	1.8 (0.89, 2.8)	0.00016
		0 copies	10.7 (9.1, 11.7)	2.9 (1.4, 4.4)	0.00012

Metabolite	Statistical Model	*AS3MT* Haplotype[b]	Mean (95% CI)[c]	β (95% CI)	p
DMA	Model 1	2 copies	81.2 (79.8, 82.7)		
		1 copy	77.2 (75.6, 78.7)	-4.1 (-6.2, -2.0)	0.00017
		0 copies	74.1 (71.2, 77.0)	-7.2 (-10, -3.9)	0.000023
	Model 2	2 copies	81.2 (79.8, 82.6)		
		1 copy	77.2 (75.6, 78.7)	-4.0 (-6.1, -1.9)	0.00022
		0 copies	74.1 (71.2, 77.1)	-7.1 (-10, -3.8)	0.000032
	Model 3	2 copies	81.2 (79.8, 82.6)		
		1 copy	77.2 (75.6, 78.7)	-4.0 (-6.1, -1.9)	0.00026
		0 copies	74.1 (71.2, 77.2)	-7.0 (-10, -3.7)	0.000050
	Model 4	2 copies	81.2 (79.8, 82.6)		
		1 copy	77.2 (75.6, 78.7)	-4.0 (-6.1, -1.9)	0.00024
		0 copies	74.1 (71.2, 77.1)	-7.1 (-10, -3.7)	0.000041
	Model 5	2 copies	81.2 (79.8, 82.6)		
		1 copy	77.2 (75.6, 78.8)	-4.0 (-6.2, -1.8)	0.00032
		0 copies	74.0 (71.0, 77.2)	-7.1 (-10, -3.7)	0.000056
	Model 6	2 copies	81.2 (79.8, 82.7)		
		1 copy	77.2 (75.6, 78.8)	-4.1 (-6.2, -1.9)	0.00026
		0 copies	74.1 (71.1, 77.1)	-7.1 (-10, -3.8)	0.000036
	Model 7	2 copies	81.2 (79.7, 82.6)		
		1 copy	77.1 (75.6, 78.8)	-4.0 (-6.1, -1.9)	0.000029
		0 copies	74.1 (71.2, 77.2)	-7.0 (-10, -3.6)	0.000058
	Model 8	2 copies	81.2 (79.8, 82.6)		
		1 copy	77.2 (75.6, 78.7)	-4.0 (-6.1, -1.9)	0.00024
		0 copies	74.1 (71.2, 77.1)	-7.0 (-10, -3.7)	0.000041

[a] Multivariable regression Model 1: Arsenic (As) metabolite (%iAs or %DMA or %MMA) = α+ β**AS3MT* haplotype

Model 2: As metabolite = α+ β**AS3MT* haplotype + γ*U-As (ln transformed).

Model 3: As metabolite = α+ β**AS3MT* haplotype + γ*U-As (ln) + λ**N6AMT1* (rs1997605).

Model 4: As metabolite = α+ β**AS3MT* haplotype + γ*U-As (ln) + λ**N6AMT1* (rs2205449).

Model 5: As metabolite = α+ β**AS3MT* haplotype + γ*U-As (ln) + λ**N6AMT1* (rs2705671).

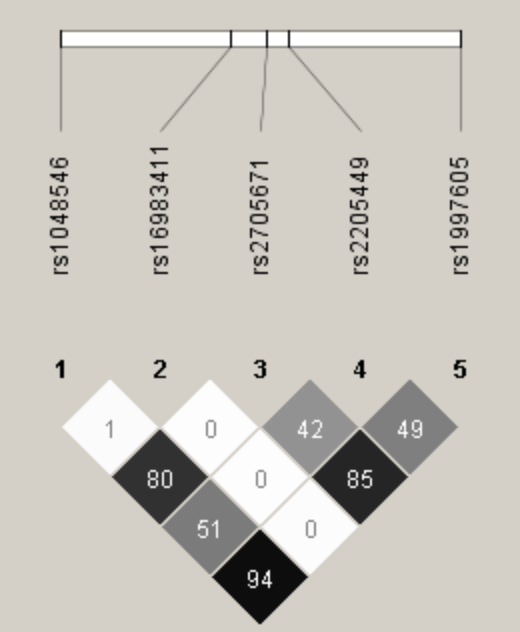
Model 6: As metabolite = α+ β**AS3MT* haplotype + γ*U-As (ln) + λ**N6AMT1* (rs16983411).

Model 7: As metabolite = α+ β**AS3MT* haplotype + γ*U-As (ln) + λ**N6AMT1* (rs1048546).

Model 8: As metabolite = α+ β**AS3MT* haplotype + γ*U-As (ln) + λ**N6AMT1* Haplotype 1.

[b] The haplotype associated with lower %MMA is denoted first and used as reference group.

[c] Mean values and 95% confidence intervals are adjusted values based on the presented statistical model.



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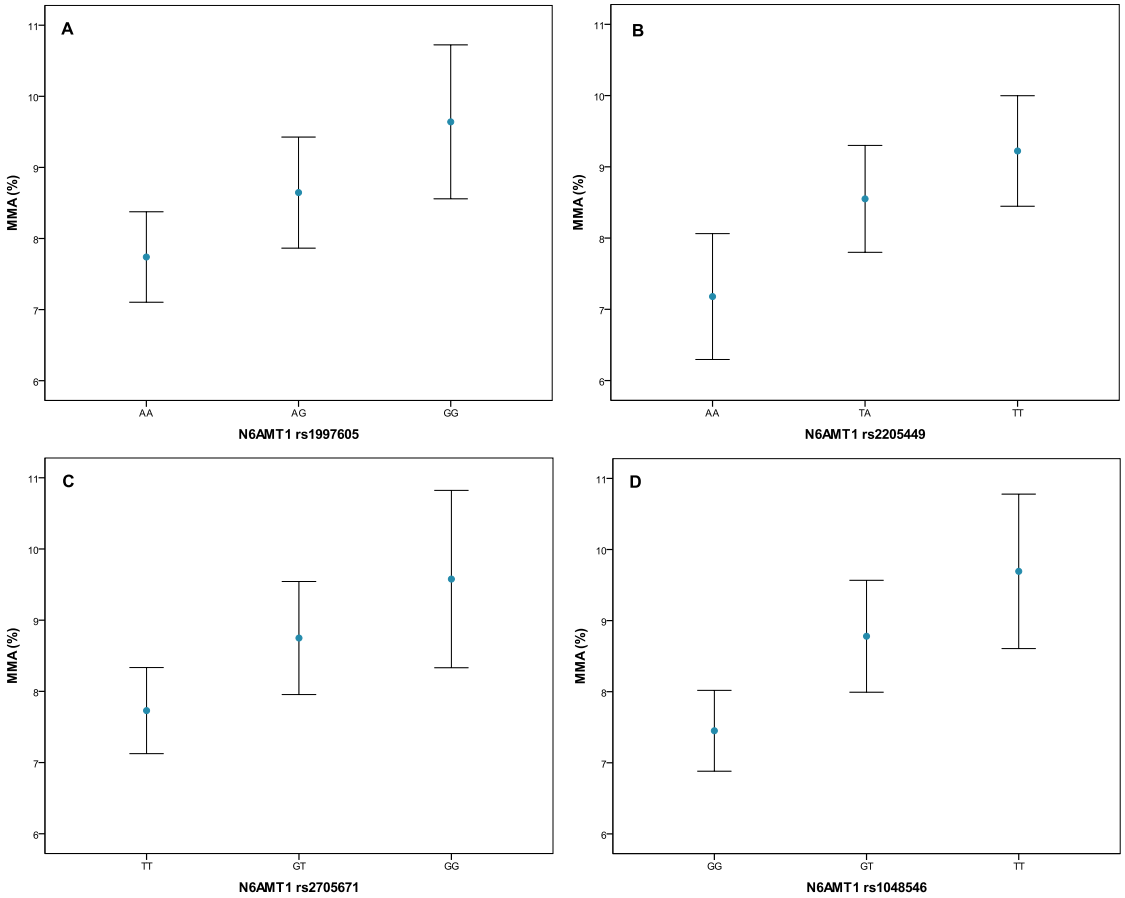

Supplemental Material Figure S2. Error bar plots. MMA fractions in urine (study population, N=188) stratified for *N6AMT1* genotypes of the following SNPs: A) rs1997605, B) rs2205449, C) rs2705671, and D) rs1048546. Error bars represent 95% confidence intervals. Numeric data are provided in Table 3.