

The gender-specific association of the putative fructose transporter *SLC2A9* variants with uric acid levels is modified by BMI

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Objective: High serum uric acid (UA) levels lead to gout and were reported to be associated with an increased risk for hypertension, obesity, metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease. Recently, the putative fructose transporter *SLC2A9* was reported to influence UA levels. The aim of the present study was to examine the association of four single nucleotide polymorphisms (SNPs) within this gene with UA levels and whether this association is modified by obesity.

Research Design and Methods: Four SNPs within *SLC2A9* (rs6855911, rs7442295, rs6449213 and rs12510549) were genotyped in the population-based prospective Bruneck Study (n=800) and in a case-control study from Utah including 1038 subjects recruited for severe obesity and 831 controls.

Results: We observed highly significant associations between all four polymorphisms with UA levels in all study groups. Each copy of the minor allele decreased age- and gender-adjusted UA levels on average by 0.30-0.35 mg/dl which translates to a relative decrease of 5-6% with p-values ranging from 10^{-9} to 10^{-11} in the combined analysis. An extended adjustment for BMI, creatinine, gout medication and alcohol intake improved p-values ranging from 10^{-14} to 10^{-20} . The association was more pronounced in women and the population-based Bruneck Study and was significantly modified by BMI with stronger effect sizes in individuals with high BMI.

Conclusions: Genetic variants within *SLC2A9* have significant effects on UA levels and are modified by gender and BMI.

In humans, uric acid (UA) is the end product of the purine metabolism and hyperuricemia might be caused by an overproduction or by disturbances in the elimination of UA. Although some experimental evidence supports a beneficial role of UA by its strong antioxidative properties (1), a number of epidemiological studies reported an association between high UA levels and cardiovascular disease, hypertension, kidney disease, metabolic syndrome (MS) and even total mortality (2,3). UA levels are furthermore positively associated with serum glucose in healthy subjects (4), and subjects with higher UA levels are at higher risk of developing type 2 diabetes mellitus (T2DM) or MS (5). However, the mechanisms underlying this association are still unclear.

The regulation of UA levels is under strong genetic control with heritability estimates ranging from 25% to 70% (6,7). The elucidation of the genetic contributors to UA levels as an intermediate phenotype for various diseases might shed some light on the pathogenesis of these complex phenotypes and might help identify new targets for treating undesirably high UA levels.

Recent genome-wide association studies identified a strong association of UA levels with genetic variants within *SLC2A9* (8-11), a gene located in the chromosomal region 4p16.1 encoding a putative fructose transporter. There is strong evidence from both animal models and human studies supporting fructose as a highly lipogenic nutrient that contributes to tissue insulin insensitivity, metabolic disturbances, and the development of a prediabetic state when consumed in high quantities (12).

In the present study we aimed to replicate the recently discovered association between genetic variation within the *SLC2A9* gene and UA concentrations in the population-based Bruneck Study. This analysis was extended

by a large case-control study of severely obese individuals from Utah, who showed increased UA levels when compared to controls, with a view to explore whether the genetic association is modified by obesity.

RESEARCH DESIGN AND METHODS

Study Populations: Bruneck Study. The Bruneck Study is a prospective population-based survey designed to investigate the epidemiology and pathogenesis of atherosclerosis (13). Briefly, the study population was recruited as a sex- and age-stratified random sample of all inhabitants of Bruneck, Italy (125 women and 125 men in the 5th to 8th decades each, n=1000). At the 1990 baseline, 93.6% of recruited subjects participated, with data assessment completed in 919 subjects. Follow-up examinations were performed 1995, 2000 and 2005. Detailed information on prevalent and incident metabolic syndrome components, diabetes mellitus and cardiovascular events is available from all examinations. The present analysis focuses on the 1995 reexamination and the follow-up period for clinical events between 1995 and 2005. In 1995, the study population still consisted of 826 subjects (96.5% of those alive). Sufficient DNA was available for 800 participants.

Obesity case-control study from Utah. The study included 1869 individuals from two groups of subjects gathered in the region of Utah. The study population was composed of 1038 subjects recruited for severe obesity ("severe obesity group" with a BMI between 33 and 92 kg/m²) and a general population sample of 831 persons with the same ethnicity ("controls"). The two groups of subjects were described in detail elsewhere (14). Briefly, the 1038 subjects with severe obesity were either seeking gastric bypass surgery or were randomly chosen from a population-based sample of severely obese participants. The examination of patients undergoing gastric

bypass surgery was done prior to the intervention. The control group consisted of 831 individuals from the same geographical region and was found to be representative of the Utah population spanning the entire BMI range.

Metabolic Syndrome and Type 2 Diabetes Mellitus: Prevalent T2DM was considered present if a prior physician diagnosis had been made or if the fasting blood glucose upon screening was ≥ 126 mg/dl or when insulin sensitizing agents or diabetes medications were taken by the individual. MS was defined according to the scientific statement from the American Heart Association and the National Heart, Lung, and Blood Institute (15). The incidence of T2DM and MS was assessed in the Bruneck Study from the 1995 to the 2005 examination.

Laboratory Methods: In both study populations, blood samples were collected after an overnight fasting period. UA levels were measured using enzymatic-colorimetric methods (Bruneck Study: MERCK, Vienna, Austria; Utah Study: Roche, USA) with intraassay and interassay coefficients of variation below 2%. Other clinical-chemical parameters were measured as described recently (14).

Four SNPs with genome-wide p-values below 10^{-7} in the data from Li et al. and Döring et al. (8,10) were selected for genotyping using a 5' nuclease allelic discrimination (Taqman) assay (Applied Biosystems, Foster City, CA, USA): rs6855911, rs7442295, rs6449213 and rs12510549. Genotyping was done within the Genotyping Unit of the Gene Discovery Core Facility at the Innsbruck Medical University, Austria.

Statistical and bioinformatic analysis: To compare characteristics between individual groups, we applied t-tests, Wilcoxon tests and Pearson's χ^2 -tests. Spearman correlation coefficients described the correlation between UA levels and components of the MS. A chi-square test for violation of the Hardy-

Weinberg equilibrium (HWE) was performed. General linear regression models were used to estimate the association of any of the four SNPs with UA levels adjusted for various covariates assuming an additive model. The additive model was applied due to a priori evidence from previous studies in various populations (8,10,11) and from the inspection of the genotype-specific means of UA levels. Interactions between the investigated SNPs and BMI on UA levels were tested by adding an interaction term (SNP*BMI) and the main covariates (sex, SNP and BMI) to the model. The effect modification was graphically illustrated for three BMI classes (<30, 30-40 and >40 kg/m²) and the three genotype levels using interaction plots applying PROC GENMOD. All statistical analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, Illinois) or SAS 9.1 (SAS Institute Inc., Cary, North Carolina).

Since all investigated polymorphisms were located in non-coding regions, their possible effect on transcription factor binding sites was evaluated in-silico using different components of the Genomatix Software Suite (Genomatix GmbH, Munich, Germany). Analyses included a search for the presence of known functional genetic elements (as e.g. promoter sequences or microRNAs) using EIDorado™ (Rel. 4.5), a search for unknown promoter-specific sequences using Promoter Inspector (Rel. 4.6) and an investigation of possible effects of the investigated polymorphisms on single transcription factor binding sites using SNPInspector (Rel. 4.6).

RESULTS

Baseline clinical characteristics and laboratory data of the study groups from Bruneck and Utah are reported in Table 1. The Utah group was also analyzed stratified by the case-control status (severe obesity versus controls).

All four SNPs were found to be in Hardy-Weinberg equilibrium in all analyzed groups

($p > 0.1$) and the genotyping efficiency ranged between 97% and 98.5%. We observed no difference in genotype frequencies between the Bruneck and Utah studies ($p > 0.1$).

Association of Genetic Variation within SLC2A9 and Uric Acid Levels: Age- and gender-adjusted linear regression models revealed a strong and highly significant association of each of the four SNPs with UA levels (Table 2) in all study groups, which was strongest in the population-based Bruneck Study. This association can clearly be described by an additive model: each copy of the minor allele lowered UA levels on average by 0.30-0.35 mg/dl representing a relative decrease of 5-6% with p-values ranging from 10^{-9} to 10^{-11} in the combined analysis.

Gender-specific Associations between SLC2A9 and Uric Acid Levels: A gender-stratified analysis revealed much stronger associations between the four SNPs and UA levels in women than in men (Table 2). This observation was most pronounced in the population-based Bruneck Study where the effect estimates for each minor allele were up to twice as high in women compared to men. Considering the fact that women on average have 20% lower UA levels compared to men, the effect differences get even more meaningful.

Interaction with BMI: The associations of the four SNPs with UA levels became stronger after additional adjustments for BMI, creatinine, gout medication and alcohol intake with p-values ranging from 10^{-14} to 10^{-20} (Table 2). BMI was the variable which most contributed to the change in p-values. Thus we investigated whether BMI was an effect modifier of the SNP-UA association by introducing besides BMI and SNP an interaction term BMI*SNP to the model. This analysis was done by combining all three groups but with adjustments for age, sex and population (Bruneck versus Utah). The interaction was significant for three of the

four SNPs ($p = 0.023-0.035$) and borderline significant for rs12510549 ($p = 0.053$). Figure 1 graphically illustrates these interactions for BMI groups < 30 , $30-40$ and > 40 kg/m².

Association with Metabolic Syndrome and T2DM: We observed significant correlations between UA levels and each singular MS component, as well as with the sum of the components (Table 3). These correlations were seen in all three groups of subjects. Age- and sex-adjusted UA levels were significantly higher in subjects with MS compared to those without. With the exception of the severe obesity group, UA levels were also significantly higher in subjects with T2DM compared to those without (Table 3). UA levels were significantly associated with the development of either a MS and/or T2DM in the Bruneck Study from the 1995 to the 2005 examination. However, no association between the four SNPs with prevalent or incident MS or T2DM could be established.

Bioinformatics: Putative transcription factor binding sites were predicted for three of the four polymorphisms (five for rs12510549, two for rs6449213 and one for rs7442295), although no biologically obvious candidates could be found. The predicted candidates mainly belonged to pathways not directly connected with the investigated phenotypes, such as cellular growth (E2F) or immune response (PAX5, BCL6, NFAT and NR2F) (data not shown).

For the polymorphism rs12510549 the generation or disruption of five different putative binding sites was predicted. Among these, a putative binding site for NFAT-Factors was recognized. NFAT-Factors have been implicated in various roles during development and adaptation of several mammalian cells outside the immune system (16).

DISCUSSION

We observed a strong gender-specific association of genetic variation within the *SLC2A9* gene and UA concentrations. The finding was most pronounced in the population-based Bruneck Study and was replicated in severely obese and control individuals from Utah. This association was modified by BMI in a way that increasing BMI amplified effects of genetic variants on UA levels.

SLC2A9 was recently identified by four independent genome-wide association studies to be strongly associated with UA levels (8-11). *SLC2A9* encodes a putative hexose transporter which probable substrate is fructose (17). Fructose intake has been described as an important contributor to UA levels and gout (18,19), as the ADP generated during the phosphorylation of fructose is used for rapid production of UA (20). Epidemiological data showed that increased total fructose intake correlated with increasing incidence of obesity, MS (21) and gout (19). Over the past decades, a general increase in UA levels was observed and it was hypothesized that a fructose-induced hyperuricemia might be in part responsible for the rise in MS (12,22,23). The detection of genes that determine UA levels by influencing the fructose metabolism would therefore be of interest. The actual mechanism how genetic variation within *SLC2A9* modulates UA levels is not fully elucidated. One possibility would be an influence on the hepatic uptake of fructose and production of uric acid. On the other hand *SLC2A9* variants were associated with low fractional excretion of UA in various population samples and experiments in *Xenopus laevis* oocytes showed that it has not only fructose but also strong uric acid transport activity (11).

It is important to note that we did not find an association between the genetic variants within the *SLC2A9* gene and prevalent as well as incident MS or T2DM. This is intriguing

given the pronounced association between the genetic variants and UA levels and despite the strong association of UA levels and these diseases in our as well as in earlier studies. This might be explained on the one hand by lack of power since the variance of serum UA levels explained by the investigated genotypes in population-based studies was about 1.2% in men and 6% in women (10) and the fraction of these two diseases explained by UA levels was also small. On the other hand, it cannot be ruled out that UA level is a surrogate marker of the disease without being in the causal pathway. However, recent studies in rats showed that fructose-induced MS is partially prevented by lowering UA levels and that the reduction of endothelial nitric oxide bioavailability by UA may be a mechanism for insulin resistance and hypertension (23). A proof of a causal association of UA with disease endpoints might be possible by the application of a Mendelian randomization approach. However, this will probably need several thousands of examined individuals. Homozygotes of the wildtype and of the rare allele differ in UA levels by 0.64-0.81 mg/dl which corresponds to 11-13% of the mean levels. Based on the findings in an earlier studies, such a difference in UA levels would change the rate of cardiovascular events by 1%.

A recent study with a systematic investigation of gender-specific differences of literature-reported genetic effects on various phenotypes documented that only one out of 432 sex-difference claims was consistently replicated in at least two other studies (24). The association of genetic variants within *SCL2A9* with UA levels clearly adds to this list, since much stronger associations were found in women than in men in five populations of the previous studies (10,11) and in three population samples of the present study. How obesity modulates the association between *SLC2A9* variants and UA levels remains to be determined. It could be related

to the higher fructose intake in obese subjects (22) and a different saturation capacity of fructose transport dependent on the genotype.

In summary, our study shows a strong association of genetic variants within the *SLC2A9* gene and uric acid levels that is modified by gender and BMI.

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Table 1: Clinical and laboratory data of participants of the Bruneck Study (n=800) and the Utah Study (n=1869) with stratification in patients with severe obesity and controls.

	Bruneck	Utah	
	(n = 800)	Controls (n=831)	Severe obesity (n=1038)
Age, yrs	62.7±11.1	52.8±8.5	44.4±11.4 ^b
Gender: male/female, n (%)	398/402 (49.8/50.2)	403/428 (48.5/51.5)	193/845 (18.6/81.4) ^b
rs12510549: TT/TC/CC	n 506/243/35	519/265/33	633/335/43
(%)	64.5/31.0/4.5	(63.5/32.4/4.1)	(62.6/33.1/4.3)
MAF	20.0%	20.3%	20.8%
rs6449213: TT/TC/CC(%)	n 517/237/30	539/259/20	648/319/40
(%)	65.9/30.2/3.8	(65.9/31.7/2.4)	(64.3/31.7/4.0)
MAF	18.9%	18.3%	19.8%
rs6855911: AA/AG/GG	n 462/283/43	471/304/43	526/412/69
(%)	58.6/35.9/5.5	(57.6/37.2/5.2)	(52.2/40.9/6.9)
MAF	23.4%	23.8%	27.3%
rs7442295: AA/AG/GG	n 494/257/34	501/287/28	595/366/49
(%)	62.9/32.7/4.3	(61.4/35.2/3.4)	(58.9/36.2/4.9)
MAF	20.7%	21.0%	23.0%
Uric acid [mg/dL]	4.7±1.3	5.5±1.5	6.3±1.5 ^b
Body mass index [kg/m ²]	25.6±3.8	27.6±4.9	46.0±7.6 ^b
Creatinine [mg/dL]	0.94±0.19	0.92±0.31	0.81±0.22 ^b
Total cholesterol [mg/dL]	230.0±42.6	187.1±34.0	186.8±36.2
LDL cholesterol [mg/dL]	145.5±37.9	105.1±27.7	108.2±27.6 ^a
HDL cholesterol [mg/dL]	58.7±16.2	50.1±15.0	45.9±11.0 ^b
Triglycerides [mg/dL]	131.7±71.9	156±105	186±106
[25 th , 50 th , 75 th percentile]	[81, 111, 158]	[86, 121, 169]	[164, 119, 223] ^b
Systolic blood pressure [mmHg]	148.3±20.7	121.5±16.7	127.3±18.5 ^b
Diastolic blood pressure [mmHg]	87.1±9.2	73.0±10.5	71.9±10.8 ^a
Glucose [mg/dL]	102±24	91±18	104±33 ^b
Metabolic syndrome, n (%) ^c	261 (32.6)	267 (32.1)	766 (73.8) ^b
Metabolic factors, median (IR) ^{d,e}	2.0 (2)	2.0 (2)	3.0 (2) ^b
Diabetes mellitus, n (%)	76 (9.5)	55 (6.6)	225 (21.7) ^b
Use of gout medication, n (%)	13 (1.6)	7 (0.8)	11 (1.1) ^a
Use of lipid lowering drugs, n (%)	25 (3.1)	64 (7.7)	122 (11.9) ^b

Values are provided as mean and standard deviation if not indicated otherwise.

^a p<0.05, ^b p<0.001 for comparison between severely obese subjects and controls from Utah.

^c Definition according to the scientific statement from the American Heart Association and the National Heart, Lung, and Blood Institute (15). Three of the following five parameters had to be present: elevated waist circumference ≥102cm in men and ≥88cm in women; elevated triglycerides ≥150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides; reduced HDL-cholesterol <40 mg/dl (1.03 mmol/l) in men, <50 mg/dl (1.3 mmol/l) in women or on drug treatment for reduced HDL-cholesterol; hypertension: ≥130mm Hg systolic blood pressure or ≥85mm Hg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension; elevated fasting glucose ≥100 mg/dl or on drug treatment for elevated glucose.

^d Metabolic factors: average number of factors considered in the definition of metabolic syndrome (see footnote above).

^e IR defined as Interquartile Range

Table 2: Association between uric acid levels and SNPs in *SLC2A9* in the Bruneck Study and the Utah Study.

SNP	Study	Men and Women							Men		Women	
		Uric acid (mg/dl) ^b			β^a	P ^a	β^b	P ^b	β^c	P ^c	β^c	P ^c
		AA	Aa	aa								
rs12510549	Bruneck	4.86±0.047	4.43±0.068	4.21±0.180	-0.319	1.86x10 ⁻⁵	-0.381	1.51x10 ⁻⁸	-0.428	2.93x10 ⁻⁵	-0.352	4.74x10 ⁻⁵
	Utah: entire group ^d	6.20±0.044	5.93±0.061	5.23±0.179	-0.300	1.31x10 ⁻⁷	-0.350	2.79x10 ⁻⁸	-0.225	0.068	-0.397	5.81x10 ⁻⁸
	controls	5.52±0.068	5.11±0.096	4.79±0.330	-0.263	9.47x10 ⁻⁴	-0.402	9.91x10 ⁻⁵	-0.212	0.186	-0.611	2.44x10 ⁻⁵
	obese	6.43±0.054	6.23±0.075	5.45±0.209	-0.326	4.39x10 ⁻⁵	-0.324	2.09x10 ⁻⁵	-0.196	0.278	-0.397	2.74x10 ⁻⁵
	Combined ^d	5.71±0.033	5.39±0.047	4.87±0.132	-0.306	3.67x10 ⁻⁹	-0.357	5.80x10 ⁻¹⁴	-0.309	9.78x10 ⁻⁵	-0.392	3.21x10 ⁻¹¹
rs6449213	Bruneck	4.86±0.046	4.44±0.068	3.99±0.192	-0.403	8.60x10 ⁻⁸	-0.427	3.54x10 ⁻¹⁰	-0.384	1.79x10 ⁻⁴	-0.492	2.00x10 ⁻⁸
	Utah: entire group ^d	6.21±0.043	5.87±0.062	5.07±0.191	-0.335	1.40x10 ⁻⁸	-0.423	5.58x10 ⁻¹¹	-0.311	0.015	-0.459	9.25x10 ⁻¹⁰
	controls	5.55±0.066	5.00±0.097	4.57±0.422	-0.281	9.55x10 ⁻⁴	-0.537	8.34x10 ⁻⁷	-0.431	0.014	-0.688	2.04x10 ⁻⁸
	obese	6.45±0.054	6.19±0.076	5.30±0.216	-0.373	4.12x10 ⁻⁶	-0.384	6.74x10 ⁻⁷	-0.205	0.258	-0.459	9.44x10 ⁻⁷
	Combined ^d	5.72±0.032	5.35±0.047	4.68±0.141	-0.357	2.33x10 ⁻¹¹	-0.428	1.13x10 ⁻¹⁸	-0.326	5.18x10 ⁻⁵	-0.489	5.84x10 ⁻¹⁶
rs6855911	Bruneck	4.90±0.048	4.49±0.062	3.99±0.161	-0.383	5.50x10 ⁻⁸	-0.432	1.13x10 ⁻¹¹	-0.411	1.64x10 ⁻⁵	-0.479	8.00x10 ⁻⁹
	Utah: entire group ^d	6.26±0.048	5.93±0.056	5.30±0.141	-0.340	1.84x10 ⁻¹⁰	-0.407	4.08x10 ⁻¹²	-0.289	0.012	-0.445	6.05x10 ⁻¹¹
	controls	5.56±0.072	5.11±0.089	4.85±0.253	-0.280	2.11x10 ⁻⁴	-0.411	1.54x10 ⁻⁵	-0.303	0.047	-0.548	1.95x10 ⁻⁶
	obese	6.51±0.060	6.22±0.068	5.51±0.166	-0.389	1.62x10 ⁻⁷	-0.401	1.70x10 ⁻⁸	-0.262	0.118	-0.445	4.90x10 ⁻⁸
	Combined ^d	5.76±0.035	5.40±0.043	4.81±0.109	-0.319	5.74x10 ⁻¹¹	-0.413	1.76x10 ⁻²⁰	-0.332	7.86x10 ⁻⁶	-0.463	6.39x10 ⁻¹⁷
rs7442295	Bruneck	4.88±0.047	4.45±0.066	4.04±0.182	-0.382	2.45x10 ⁻⁷	-0.424	2.34x10 ⁻¹⁰	-0.366	3.36x10 ⁻⁴	-0.503	4.00x10 ⁻⁹
	Utah: entire group ^d	6.23±0.046	5.90±0.059	5.28±0.172	-0.301	1.15x10 ⁻⁷	-0.385	6.48x10 ⁻¹⁰	-0.264	0.029	-0.428	3.59x10 ⁻⁹
	controls	5.56±0.069	5.04±0.092	4.82±0.346	-0.260	1.27x10 ⁻³	-0.482	3.23x10 ⁻⁶	-0.371	0.023	-0.674	1.44x10 ⁻⁷
	obese	6.46±0.057	6.22±0.072	5.50±0.198	-0.335	2.08x10 ⁻⁵	-0.349	3.33x10 ⁻⁶	-0.148	0.402	-0.428	3.03x10 ⁻⁶
	Combined ^d	5.74±0.034	5.37±0.045	4.82±0.129	-0.308	2.61x10 ⁻⁹	-0.401	1.76x10 ⁻¹⁷	-0.299	1.52x10 ⁻⁴	-0.465	2.01x10 ⁻¹⁵

Values are provided as mean and standard error

^a Adjusted for age and gender

^b Adjusted for age, gender, body mass index, creatinine, alcohol consumption, and gout medication

^c Adjusted for age, body mass index, creatinine, alcohol consumption, and gout medication

^d Additionally adjusted for group status (severe obese versus controls)

Table 3: Correlation of uric acid levels with parameters of the metabolic syndrome and type 2 diabetes mellitus.

	Bruneck	Utah	
	(n = 800)	Controls (n=831)	Severe obesity (n=1038)
Correlation coefficients between uric acid and ...			
BMI	0.29 ^c	0.44 ^c	0.17 ^c
Glucose	0.28 ^c	0.31 ^c	0.09 ^b
Systolic blood pressure	0.15 ^c	0.25 ^c	0.08 ^a
Diastolic blood pressure	0.11 ^b	0.29 ^c	0.01
HDL cholesterol	-0.29 ^c	-0.44 ^c	-0.20 ^c
Triglycerides	0.38 ^c	0.33 ^c	0.14 ^c
Metabolic syndrome components	0.31 ^c	0.39 ^c	0.18 ^c
Uric acid concentrations in subjects ...			
with and without metabolic syndrome	5.3±1.4 vs. 4.3±1.2 ^c	6.2±1.4 vs. 5.2±1.4 ^c	6.4±1.5 vs. 6.0±1.5 ^c
with and without T2DM	5.0±1.5 vs. 4.7±1.3 ^a	6.1±1.4 vs. 5.5±1.5 ^b	6.3±1.7 vs. 6.3±1.5

^a p<0.05, ^b p<0.01, ^c p<0.001.

Figure 1: Interaction plots describing the effect modification of BMI on the association of the four investigated *SLC2A9* SNPs with uric acid levels. The x-axis displays the allelic status of the respective SNP; the y-axis corresponds to the predicted probability that a person with the respective genotype exceeds the gender-specific median of uric acid levels given the specific BMI class. The quantitative interactions are represented as lines, with statistically significant differing slopes in all but one SNP (rs12510549). AA, Aa and aa denote the three possible genotypes: wildtype, heterozygote carriers and homozygotes for the minor allele.

