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Genetic Contributions to Urgency Urinary Incontinence in Women

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Abstract

Purpose—To identify genetic variants associated with urgency urinary incontinence (UUI) in post-menopausal women.

Materials and Methods—A two-stage genome wide association analysis was conducted to identify variants associated with UUI. The Women's Health Initiative-Genomics & Randomized Trials Network (GARNET) sub-study with 4,894 genotyped post-reproductive white women was randomly split into independent discovery and replication cohorts. Genome-wide imputation was performed using IMPUTE2 with the 1000-Genomes-ALL-Phase-I integrated variant set as a reference. Controls reported no UUI at enrollment or follow-up; cases reported monthly or greater UUI and leaked sufficiently to wet/soak underpants/clothes. Logistic regression models were used

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to predict UI case versus control status based on genotype, assuming additive inheritance. Age, obesity, diabetes and depression were included in the models as covariates.

Results—Following quality control, 975,508 single nucleotide polymorphisms (SNPs) in 2,241 cases (discovery=1,102, replication=1,133) and 776 controls (discovery=405, replication=371) remained. Genotype imputation resulted in 9,077,347 SNPs and insertions/deletions with minor allele frequency >0.01 available for analysis. Meta-analysis of the discovery and replication samples identified six loci on chromosomes 5, 10, 11, 12 & 18 associated with UI at $p < 10^{-6}$. Three of the loci were within genes, the zinc finger protein 521 (*ZFP521*) gene on chromosome 18q11, the *ADAMTS16* gene on chromosome 5p15, and the *CIT* gene on chromosome 12q24. The other three loci were intergenic.

Conclusions—Although environmental factors also likely contribute, this first exploratory Genome-Wide Associated Study (GWAS) for UI suggests that genetic variants in the *ZFP521*, *CIT*, and *ADAMTS16* genes might account for some of the observed heritability of the condition.

Keywords

Genome-wide association study; GWAS; Urgency urinary incontinence; UI

Introduction

Urgency urinary incontinence (UI) is a common debilitating and costly condition in women: overall prevalence rates range from 20% to 36.4%, depending on the population queried and the case definition.^{1,2} The etiology of UI is unclear but it may derive from inflammatory, muscular or neurologic abnormalities. In addition to environmental contributions, a population-based twin study reported a formal heritability associated with the development of urinary incontinence, frequency and nocturia.³ In another study of 1168 female twin pairs [548 monozygotic and 620 dizygotic] from middle-aged (46-68 years) and older (70-94 years) cohorts, the proband concordance rates for UI were higher for monozygotic twins compared to dizygotic twins in both middle-aged as well as older twins.⁴

Genome wide association studies (GWAS) offer a powerful research approach to identify common variants associated with a disease or trait. GWAS case control studies can rapidly and cost-effectively evaluate thousands of single nucleotide polymorphisms (SNPs) to identify genetic differences in people with specific medical conditions compared to those without. A recent systematic review and meta-analysis reported moderate epidemiologic credibility for genetic associations with overactive bladder and prolapse.⁵ Ultimately the goal of such information is to understand the pathophysiology of the condition and thereby improve treatment and prevention.

The Women's Health Initiative (WHI) has significantly contributed to our understanding of postmenopausal hormone therapy and also collected extensive phenotypic information including urinary incontinence history. Genotypic data have been generated for select WHI subgroups. The aim of the current study was to perform the first GWAS to identify genetic variants that contribute to UI using phenotypic incontinence data from white women with existing genotypic data.

Material and Methods

Genotypic and phenotypic data from the WHI GARNET sub-study were used to conduct a two-stage (discovery and replication) GWAS analysis of UUI. Institutional Review Board approval was obtained for review of WHI data. Controls were WHI participants who had never experienced urinary incontinence (UI) at enrollment and did not develop UUI during the study. Cases were defined as women who at any time during the study reported they had symptoms of UUI more than once a month and who leaked sufficiently to wet or soak their underpants or clothes (Table 1). Covariates included the following characteristics: age, defined as the participant's age at enrollment and treated as a continuous variable; obesity, defined as body mass index greater than or equal to 30; diabetes, defined as reporting being told by a doctor they had diabetes; and depression, defined as a score > 0.06 on the Center for Epidemiologic Studies Depression Scale short form.⁶ Twenty-five women with a neurological condition were excluded as UUI in this population may be the result of their underlying condition.

The GARNET study genotyped 4,894 women with the Illumina Omni Quad 1.0M chip. Genotyping quality control was conducted by the genotyping center, Broad Institute, and the GARNET data coordinating center, the University of Washington. We applied the following additional quality control measures: exclusion of individuals with a missing call rate >3%, with less than 75% European ancestry in a Structure⁷ analysis using the HapMap 3 CEU population as a reference,⁸ or with values greater than 3 standard deviations away from the sample mean for any of the first three eigenvectors calculated using Eigenstrat.⁹ The Eigenstrat analysis identifies individuals whose ancestry is significantly different than that of most of the study population. Eleven pairs of full or half siblings were identified; for each pair, we excluded the individual with the lower SNP call rate. Single nucleotide polymorphisms (SNPs) were excluded if they deviated significantly from Hardy-Weinberg equilibrium ($p < 0.0001$).

To increase the number and type of genetic polymorphisms examined, genome-wide imputation of SNPs and insertion/deletion polymorphisms (indels) was performed. Prior to imputation, the observed genotypes were pre-phased using SHAPEIT v2¹⁰ to estimate haplotypes. Imputation of genotypes was performed using IMPUTE2 v2.3.0¹¹ with reference to the December, 2013 release of 1000 Genomes ALL Phase I integrated variant set haplotype panel,¹² which contains haplotypes from 1,092 subjects. Variants with a minor allele frequency (MAF) of 0.01 or less were filtered out post-imputation.

For primary association analyses, subjects were randomly assigned to discovery and replication samples. One degree of freedom logistic regression models were run using ProbABEL¹³ to predict UUI case versus control status relative to genome-wide genotype dosages assuming an additive mode of inheritance. Age, obesity, diabetes, and depression were included as covariates in the model. Meta-analysis of the discovery and replication samples was conducted using METAL.¹⁴ Q-Q plots were developed to examine the probability distributions of the association results, where a lambda of 1 indicates observed distribution exactly matches the expected distribution. Based on the GARNET cohort prevalence of UUI (52%), a genotype relative risk of 1.30 for a variant with minor allele

frequency of 30% could be detected in the discovery or validation cohorts with 86% power using an alpha level of 5×10^{-8} (Power Calculator for Genetics Studies).¹⁵

Pathway analyses were conducted to identify potential biological pathways whose genes contain the SNPs and other variants found to be associated with UUI. We performed these analyses using both an association method, [adaptive rank product truncation (ARTP) as implemented in the ARTP R package],¹⁶ and a competitive method, gene set enrichment analysis (GSEA) as adapted for GWAS¹⁷ in GenGen.¹⁸ To generate the input for ARTP and GenGen, we combined the discovery and replication samples, with linkage disequilibrium pruned SNPs to reduce redundancy resulting from high correlation among variants, and performed association testing for the UUI case/control phenotype as described above. Ten thousand permutations for the association test were conducted in which UUI case/control status was randomly swapped among subjects to provide an empirical distribution of results of the pathway analysis. Variants within ± 20 kb of each gene were mapped to the gene. We tested gene sets from two sources: (1) all pathways from the Reactome database¹⁹ as of January 9, 2014 and (2) Gene Ontology²⁰ annotated Ensembl genes (release 74) downloaded via the Ensembl Biomart.²¹ Gene sets exhibiting a false discovery rate (FDR) < 0.2 in these analyses were considered significant.

Results

Excluding women with neurologic disorders, the prevalence rate of UUI in this cohort was 52.4% (2550/4869). Of the 4,894 women who were genotyped as part of the WHI GARNET Study, 706 individuals were eliminated as a result of the quality control process and an additional 1171 women did not meet the definition of case or control. Eligible women were randomized to the discovery set (n=1513) or the validation dataset (n=1504). Of these women, 2,241 met the UUI case definition (N=1,108 in the discovery and N=1,133 in the replication subsets) and 776 met the definition of control (N=405 in the discovery and N=371 in the replication subsets).

The discovery and replication data sets did not differ significantly on any clinical characteristic as summarized in Table 2. In both the discovery and replication subsets, cases were significantly more likely to be obese than controls (49% vs 31%, $p < 0.001$; 47% vs 28%, $p < 0.001$, respectively). There were no differences between cases and controls in either the discovery or replication cohorts for categories of age or level of education. Within the replication cohort, there were significant differences between cases and controls for diabetic status (6% vs 2%, $p = 0.03$), depression (13% vs 8%, $p = 0.01$), region of the country where recruited ($p = 0.006$), and level of income ($p = 0.02$). In the discovery subset, the distribution of these characteristics among the cases and controls were similar, but the differences were not significant.

SNP quality control procedures resulted in elimination of a total of 164,911 SNPs leaving a total of 975,508 genotyped SNPs. After genotype imputation, there were 9,077,347 SNPs and indels with minor allele frequency > 0.01 available for analysis. Logistic regression models were run independently in the discovery and replication cohorts to identify genetic variants associated with UUI (Table 3). Q-Q plots revealed no evidence of systemic bias,

such as population substructure, in either cohort ($\lambda=1.008$ in discovery cohort, 1.011 in replication cohort). In addition, analyses including eigenvectors as covariates to account for population substructure yielded nearly identical results (data not shown). Only one SNP in either cohort surpassed the genome-wide significance threshold level of 5×10^{-8} (an intergenic SNP on chromosome 7). Seventeen SNPs had a $p < 10^{-6}$ in the discovery cohort; 14 in the citron (*CIT*) gene, and one in the solute carrier family 16 (monocarboxylate transporter), member 7 gene (*SLC16A7*); the other two variants were intergenic. All of the SNPs with a $p < 10^{-6}$ in the replication cohort were intergenic. There was no overlap between the most significant variants in the two cohorts

The results of a meta-analysis of the discovery and replication subsets are illustrated in the Manhattan plot in Figure 1. The 17 variants most strongly associated with UII (p range 1.91×10^{-7} to 9.47×10^{-7}) represent six genomic loci on chromosomal bands 5p15, 10p12, 11q14, 12p11, 12q24 and 18q11 (Table 3). The tagged loci on chromosome 18q11 is an intron of the zinc finger protein 521 gene (*ZFP521*), which has been associated with regulation of blood, bone and neural stem cell proliferation. The tagged intron includes two histone modification sites and a transcription regulatory binding site, and is highly conserved across species. The chromosome 5p15 locus was also located within a gene, the ADAM metalloproteinase with thrombospondin type 1 motif, 16 (*ADAMTS16*) gene, which may be involved in regulation of cell proliferation. The 12q24 locus is within the citron (rho-interacting, serine/threonine kinase 21) (*CIT*) gene, which is involved in cell division and central nervous system development. One locus (10p11) is the gene for the uncharacterized long intergenic non-protein coding RNA 1516 (*LINC01516*), and two (11q14 and 12p11) are intergenic.

None of the REACTOME or Gene Ontology (GO) terms had an $FDR < 0.2$ in the ARTP-ARTP, RTP-ARTP or ARTP pathway analyses. Gene set enrichment analyses identified 1 REACTOME pathway and 3 GO terms associated with UII; 1 of the 4 in both databases (transforming growth factor [TGF]-beta/bone morphogenetic proteins [BMP] pathway), (Table 4).

Discussion

Previous studies of families and twins as well as a recent systematic review have suggested a genetic predisposition to overactive bladder and incontinence.^{3,4,5} Our meta-analysis revealed six loci that might be associated with risk of UII, including loci within the *ZFP521*, *ADAMTS16* and *CIT* genes. This association persisted with adjustment for known confounders of UII such as age, obesity, diabetes, and depression. Furthermore, the TGF- β and wound healing pathways, which were identified as being associated with UII in pathway analyses, have biologic plausibility for an involvement in the development of UII.

For complex traits such as UII where both genetics and environment influence the development of the condition, observed effect sizes for specific alleles are expected to be small, with risk ratios as low as 1.2.²² Our study was powered to detect a risk effect size of 1.3 for an allele frequency of 30%. This study required a relatively large effect in order to attain significance. This raises the possibility that true associations may have been obscured

by this study's high detection thresh-holds. Accordingly, this study's strength lies in its novelty rather than in the definitiveness of its findings.

The nominal association of variants within an intron in *ZFP521* suggests that *ZFP521* gene products or change in their expression may increase susceptibility to UUI. *ZFP521* is associated with stem cells and has been implicated in the control of blood, bone and neural progenitor cells.²³ *ZFP521* has been identified as a striatonigral-specific transcription factor that is essential for the development of striatonigral medium spiny neurons.²⁴ In humans, dysfunction and degeneration of striatonigral projections are implicated in Parkinson's disease, a condition in which detrusor overactivity is common.²⁵

The roles of the *ADAMTS16* and *CIT* genes are less clear. The *ADAMTS16* gene encodes a member of the disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) protein family, which are expressed at high levels in fetal lung and kidney and adult brain and ovary.²⁶ The *CIT* gene, on chromosome 12q24, encodes a rho interacting serine/threonine-protein kinase that has been associated with cell division, functioning to promote efficient cytokinesis. RhoA/Rho-associated kinase (ROCK) is a serine/threonine protein kinase. The expression and functional role of RhoA/Rho-kinase in the human, as well as the rat urinary bladder contractile mechanisms has been well documented and Rho-kinase inhibition can suppress bladder overactivity.²⁷ Therefore, involvement of the *CIT* gene in UUI is biologically plausible.

Gene enrichment analysis using two databases implicated the TGF-beta/BMP pathway in the development of UUI. This pathway affects cell signaling directly or through interaction with other signaling pathways such as Notch (Table 3). Notch pathways have been directly implicated in the development of the striatal compartments in the brain, providing a putative mechanism for the involvement of *ZFP521* protein in UUI.²⁸ Pathways involved in wound healing were also implicated. Events that cause injury to pelvic floor tissues may serve as inciting and/or promoting events that may result in UUI in women predisposed due to abnormal wound healing or tissue remodeling.

Because no variants surpassed the genome-wide significance p-value of 5×10^{-8} , we cannot exclude the possibility that these findings are due to random chance. However, many early hypothesis-generating GWAS studies exist using a lower significance threshold of $p=10^{-5}$ for "suggestive association".^{29,30} Further validation and confirmation of the association of the *ZFP521* gene with UUI phenotype in independent GWAS studies is required.

Potential limitations of this study include the lack of validated measures to define the UUI phenotype, the evaluation of prevalent versus incident exposure odds ratios and choice of timing for defining cases and controls. However, these issues were recognized in the early stages of study design. The first issue was addressed by carefully choosing the questions from the WHI database which defined UUI phenotype (cases) or non-UUI phenotypes (controls) which were clinically important and relevant such as frequency of leakage more than once a month and leakage that soaks underpants or outer clothes. Further, as a part of making this clear distinction between cases and controls, we wished to increase the power and reduce misclassification, therefore excluding women with leakage less than 1 per month

or leakage insufficient to wet underpants. The validity of choosing these questions is supported by the fact that they provided sufficient detail to characterize a population demographically similar to UI subjects in the literature. The UI prevalence rate in this study was similar to that reported by others for this age group; also similar to other reports, obesity and diabetes, were associated with the UI phenotype.¹

Although none of the SNPs in the discovery, validation or meta-analyses overlapped, this is common in GWA studies especially ones such as these, which have lower power. As a result, replication of association may require very large samples.

The strength of this study is that this is the first genome-wide association study for UI in a well-defined population of older, post-menopausal, non-Hispanic white women. In general, a GWAS study is most efficient statistically if cases are as homogenous as possible. In this respect, the WHI cohort provided phenotypic and genotypic data on a unique homogenous and well characterized cohort of older women. The WHI database also allowed us to control for several known important confounders or effect modifiers of genetic susceptibility to UI, including age, obesity, pregnancy history, hormone use, menopausal status, and prior hysterectomy. Therefore, although our study is limited to Caucasian women, this allowed us to limit population heterogeneity and identify genotypes associated with UI.

Conclusion

UI is a complex condition that is likely influenced by both environmental and genetic interactions. Our results have identified three potential loci that will allow for future hypothesis testing in animal models and validation studies in humans to confirm and potentially expand these findings, further enhancing the understanding of UI pathophysiology.

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Abbreviation List

UII	Urgency urinary incontinence
GARNET	Genomics & Randomized Trials Network
SNPs	Single nucleotide polymorphisms
GWAS	Genome-Wide Associated Study
WHI	Women's Health Initiative
UI	Urinary incontinence
CEU	Caucasian European from Utah
ARTP	Adaptive rank product truncation
GSEA	Gene set enrichment analysis
FDR	False discovery rate
GO	Gene ontology
TGF	Transforming growth factor
BMP	Beta/bone morphogenetic proteins
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motif
ROCK	RhoA/Rho-associated kinase

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Figure 1.
Manhattan Plot

Table 1

WHI Questions on Urinary Incontinence

1. Have you ever leaked even a small amount of urine involuntarily and you couldn't control it? *	5. What protection do you wear in case you leak urine?
a. Yes	a. None
b. No	b. Mini-pad, tissue or paper towel
2. When do you usually leak urine?*	c. Menstrual pad or shield
a. No longer leak urine	d. Diaper, towel, Attends, Depends
b. When I cough, laugh, sneeze, lift, stand up or exercise	e. Other
c. When I feel the need to urinate and can't get to a toilet fast enough	6. How often does the leakage of urine limit your daily activities?
d. When I am sleeping	a. Never
e. Other	b. Almost never
3. How often does this leaking urine occur?*	c. Sometimes
a. Not once during the past year	d. Fairly often
b. Less than once a month	e. Very often
c. More than once a month but less than once a week	7. How much does the leakage of urine bother or disturb you?
d. One or more times a week but less than every day	a. Not at all disturbing
e. Daily	b. A little disturbing
4. How much urine do you usually lose when it leaks?*	c. Somewhat disturbing
a. None	d. Very disturbing
b. Barely noticeable on underpants	e. Extremely disturbing
c. Soaked underpants	
d. Soaked through to outer clothing	

* WHI questions used to define presence of UUI

Table 2

Clinical Characteristics of the Discovery and Replication Cohorts

Characteristic	Discovery Cohort			Replication Cohort		
	Case	Control	P	Case	Control	p
Subjects (n)	1,102	405		1,133	371	
Age category (years)			0.13			0.72
50-59	17.7%	21.7%		18.1%	19.7%	
60-69	47.2%	47.4%		47.2%	47.4%	
70-79	35.1%	30.9%		34.7%	32.9%	
Obesity	49.1%	31.1%	<0.001	47.4%	28.0%	<0.001
Diabetes	5.5%	4.0%	0.33	5.5%	2.2%	0.03
Depression	10.8%	9.4%	0.41	12.6%	7.8%	0.01
Stress urinary incontinence	44.6%	0.7%	<0.001	43.1%	0.8%	<0.001
Region *			0.62			0.006
Northeast	23.8%	25.2%		22.9%	30.2%	
South	22.3%	19.3%		20.1%	22.6%	
Midwest	30.1%	31.9%		28.7%	22.1%	
West	23.7%	23.7%		28.2%	25.1%	
Education *			0.08			0.19
Some High School	6.2%	7.9%		6.4%	7.3%	
High School Graduate	24.2%	24.7%		22.2%	27.0%	
Some college	40.7%	44.4%		42.1%	40.7%	
Bachelor's Degree	7.6%	8.4%		8.7%	9.7%	
Some Graduate	20.6%	14.3%		20.0%	14.8%	
Income *			0.09			0.02
\$0-20K	25.9%	24.0%		24.4%	30.5%	
\$20-50K	49.0%	46.9%		50.0%	42.3%	
\$50-90K	17.6%	17.0%		17.8%	16.4%	
\$100+K	2.1%	3.2%		2.3%	2.4%	

* Totals do not add up to 100% as not all subjects provided information for this question.

Table 3

Associated SNPs* in the Discovery Cohort, Replication Cohort and Meta-Analysis

Marker	Chromosome	Minor allele frequency	Gene	OR (95% CI)	Genotyped/Imputed	p-value
Discovery						
rs278110	12q24	0.478	<i>CIT</i>	1.55(1.31-1.84)	Imputed	4.57E-07
rs2952444	12q24	0.477	<i>CIT</i>	1.55(1.31-1.84)	Imputed	4.59E-07
rs2952403	12q24	0.477	<i>CIT</i>	1.55(1.31-1.84)	Imputed	4.60E-07
rs148562787	11q14	0.016	-	4.81(2.61-8.88)	Imputed	4.89E-07
rs2936832	12q24	0.478	<i>CIT</i>	1.55(1.30-1.83)	Imputed	5.31E-07
rs4766947	12q24	0.478	<i>CIT</i>	1.55(1.30-1.83)	Imputed	5.33E-07
rs4767840	12q24	0.484	<i>CIT</i>	1.56(1.31-1.85)	Imputed	5.59E-07
rs4767841	12q24	0.496	<i>CIT</i>	1.55(1.31-1.84)	Imputed	5.78E-07
rs2996028	12q24	0.498	<i>CIT</i>	1.55(1.30-1.84)	Imputed	5.99E-07
rs10129003	12q24	0.476	<i>CIT</i>	1.54(1.30-1.82)	Imputed	6.15E-07
rs11064884	12q24	0.478	<i>CIT</i>	1.54(1.30-1.83)	Imputed	6.39E-07
rs6490269	12q24	0.476	<i>CIT</i>	1.54(1.30-1.82)	Imputed	6.90E-07
rs10877321	12q14	0.184	<i>SLC16A7</i>	0.54(0.43-0.69)	Imputed	6.98E-07
rs2074052	12q24	0.477	<i>CIT</i>	1.53(1.29-1.82)	Imputed	7.61E-07
rs35168868	12q24	0.475	<i>CIT</i>	1.53(1.29-1.81)	Imputed	7.95E-07
rs7294387	12q24	0.476	<i>CIT</i>	1.53(1.29-1.82)	Imputed	8.04E-07
rs10160598	11q14	0.016	-	4.48(2.46-8.16)	Imputed	9.32E-07
Replication						
rs73055256	7p21	0.029	-	3.67(2.31-5.82)	Imputed	3.52E-08
rs73065462	7p21	0.033	-	3.07(2.02-4.67)	Imputed	1.66E-07
rs74812286	9p23	0.074	-	2.18(1.62-2.93)	Imputed	3.19E-07
rs7681572	4p13	0.339	-	0.63(0.53-0.75)	Imputed	3.41E-07
rs2171423	4p13	0.34	-	0.63(0.53-0.76)	Genotyped	4.13E-07
rs4991435	4p13	0.34	-	0.63(0.53-0.76)	Imputed	4.42E-07
rs6856185	4p13	0.34	-	0.63(0.53-0.76)	Imputed	4.47E-07
rs6832265	4p13	0.34	-	0.63(0.53-0.76)	Imputed	4.50E-07
rs79628861	9p23	0.092	-	2.00(1.52-2.64)	Imputed	9.52E-07
Meta-analysis						
rs72881251	18q11	0.17	<i>ZNF521</i>	1.50(1.29-1.75)	Imputed	1.91E-07
rs148495658	18q11	0.17	<i>ZNF521</i>	1.50(1.29-1.76)	Imputed	2.04E-07
rs7704641	5p15	0.49	<i>ADAMTS16</i>	0.73(0.65-0.82)	Imputed	2.19E-07

Marker	Chromosome	Minor allele frequency	Gene	OR (95% CI)	Genotyped/Imputed	p-value
rs72881253 [†]	18q11	0.15	<i>ZNF521</i>	1.51(1.29-1.77)	Imputed	2.22E-07
rs112673195	12p11	0.10	-	1.61(1.34-1.94)	Imputed	2.64E-07
rs72881267	18q11	0.15	<i>ZNF521</i>	1.51(1.29-1.77)	Imputed	2.89E-07
rs143621834 [‡]	18q11	0.15	<i>ZNF521</i>	1.51(1.29-1.76)	Imputed	3.01E-07
rs72881254	18q11	0.15	<i>ZNF521</i>	1.51(1.29-1.76)	Imputed	3.06E-07
rs9946042 [†]	18q11	0.15	<i>ZNF521</i>	1.50(1.28-1.75)	Genotyped	3.72E-07
rs7124972	11q14	0.016	-	3.00(1.97-4.57)	Imputed	5.75E-07
rs746635	5p15	0.499	<i>ADAMTS16</i>	0.74(0.66-0.83)	Genotyped	6.00E-07
rs11746278	5p15	0.5	<i>ADAMTS16</i>	0.72(0.61-0.86)	Imputed	6.52E-07
rs150663673	10p12	0.019	<i>RP11-80K21.3</i>	4.06(1.88-8.73)	Imputed	8.17E-07
rs959693	5p15	0.498	<i>ADAMTS16</i>	0.72(0.61-0.86)	Imputed	8.64E-07
rs4767841	12q24	0.496	<i>CIT</i>	1.19(1.00-1.42)	Imputed	8.99E-07
rs12953891	18q11	0.158	<i>ZNF521</i>	1.41(1.12-1.77)	Imputed	9.06E-07
rs10160598	11q14	0.016	-	1.93(1.02-3.65)	Imputed	9.47E-07

* $p < 1 \times 10^{-6}$;

[†] histone H3 acetylation site at lysine 27 (H3k27Ac) region-intergenic

[‡] TF binding site; evolutionarily conserved²⁵

Table 4

Pathways Associated With Urgency Urinary Incontinence

Pathways Associated With Urgency Urinary Incontinence With A FDR < 0.2			
Database	Pathway or process	Description ^{23,25}	FDR
REACTOME	Signaling by TGF-beta	The TGF-beta/BMP pathway incorporates several signaling pathways that share most, but not all, components of a central signal transduction engine. The pathway plays a number of different biological roles in the control of embryonic and adult cell proliferation and differentiation, and it is implicated in a great number of human diseases. It also "cross talks" with other signaling pathways such as Notch, MAPK and WNT.	0.17
Gene Ontology	Receptor Complex		0.199
Gene Ontology	Wound healing	The series of events that restore integrity to a damaged tissue, following an injury.	0.199
Gene Ontology	Negative regulation of epithelial to mesenchymal transition.	Any process that decreases the rate, frequency, or extent of epithelial to mesenchymal transition. Epithelial to mesenchymal transition where an epithelial cell loses apical/basolateral polarity, severs intercellular adhesive junctions, degrades basement membrane components and becomes a migratory mesenchymal cell.	0.199