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Genome wide association study identifies two novel loci associated with female stress and urgency urinary incontinence

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Abstract:
Introduction: Stress and urgency incontinence are heritable, but no risk loci have been identified. We undertook a GWAS, using three European cohorts, followed by replication in six further studies, with supplementary transcriptomic analyses using human bladder biopsies.
Materials and Methods: Genotyping in discovery cohorts (n=8,979) was conducted using Illumina arrays. Replication genotyping used competitive PCR (n=4,069). Biopsies from women with urgency or stress incontinence were run on Affymetrix-U133 arrays.
Results: Discovery analyses identified five genome-wide significant loci. Two loci replicated: rs138724718 ($p=3.39x10^{-09}$) and rs34998271 ($p=1.70x10^{-09}$). In analysis of differential expression, the top-ranked process (GO:0003012, $p=7.5x10^{-10}$), includes *CHRM3* (fold difference:4.23, p=0.0007), which is the main drug target for urgency incontinence, *SULF2* (fold difference:1.52, p=0.005) in the top locus from the discovery phase, and *EDN1* (fold difference:-1.60, p=0.09) in the top locus from the replication phase.
Conclusions: We identified two genetic variants strongly associated with urinary incontinence. The first, rs138724718, is situated near *MARCO,* with a role in host defense. The second, rs34998271, is situated near *EDN1* a potent constrictor of smooth muscle*,* which was differentially expressed in bladder. This work highlights the myogenic and urotheliogenic mechanisms for incontinence, and suggests the potential of endothelin modulating drugs for urgency incontinence.

Chr	GRCh37 Position	SNP	Effect Allele	Other Allele	MAF	Phenotype	Discovery Cohorts (n=8,997)			Replication Cohorts (n=4,069)			Overall
							OR	95%CI	p	OR	95%CI	p	p
20	46424160	rs139329202	c	g	0.01	UUI	8.50	4.12-17.55	$8.07x10^{-9}$	1.35	0.82-2.21	0.238	$2.38x10^{-05}$
6	1430664	rs146033157	a	t	0.03	UUI	0.33	0.23-0.48	$1.73x10^{-8}$	0.97	0.35-2.71	0.960	n/a
14	55489229	rs146757102	a	g	0.05	UUI	0.45	0.34-0.60	$1.95x10^{-8}$	1.13	0.87-1.45	0.360	$5.12x10^{-03}$
7	141328145	rs78851245	t	c	0.02	Any UI	3.22	2.13-4.86	$2.92x10^{-8}$	1.46	1.00-21.3	0.051	$2.11x10^{-07}$
7	34354797	rs78878767	a	c	0.01	UUI	4.26	2.56-7.10	$3.04x10^{-8}$	0.86	0.51-1.43	0.556	$2.11x10^{-07}$
3	55473083	rs13059018	c	g	0.07	SUI	0.70	0.61-0.81	$1.01x10^{-7}$	1.14	1.00-1.29	0.054	$1.40x10^{-06}$
12	11049362	rs201363123	ag	a	0.06	Any UI	0.65	0.56-0.76	$1.03x10^{-7}$	1.14	1.00-1.29	0.053	$5.43x10^{-05}$
1	154881110	rs1218596	t	c	0.06	Any UI	0.64	0.55-0.75	$1.04x10^{-7}$	0.95	0.75-1.20	0.681	$4.49x10^{-06}$
11	39642765	rs10768519	a	c	0.26	UUI	0.80	0.74-0.87	$2.26x10^{-7}$	1.00	0.85-1.17	0.954	$1.40x10^{-04}$
9	105517298	rs72738866	t	c	0.26	SUI	0.79	0.71-0.87	$2.55x10^{-7}$	1.01	0.89-1.14	0.895	$5.97x10^{-05}$
2	119587824	rs138724718	a	g	0.02	SUI	1.85	1.47-2.35	$2.89x10^{-7}$	1.73	1.20-2.48	0.003	$3.39x10^{-09}$
6	12533066	rs34998271	a	g	0.05	UUI	1.70	1.40-2.07	$4.97 x10^{-7}$	1.55	1.20-2.01	0.0008	$1.70x10^{-09}$

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Author Disclosure Information:

R. Cartwright: None. **M. Jarvelin:** None. **P. Miotla:** None. **V. Khullar:** None. **P. Bennett:** None. **A. Walley:** None.
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