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Norton P[1], Nygaard I[1], Cannon-Albright L[1]
1. University of Utah School of Medicine

THE HERITABLE CONTRIBUTION TO LOWER URINARY TRACT SYMPTOMS IN WOMEN

Hypothesis / aims of study

Family history has been suggested as a major risk factor for the development of urinary incontinence, but many of these studies are hampered by ascertainment bias. We sought to determine the heritability of different phenotypes representing lower urinary tract symptoms (LUTS) in women using a unique population database.

Study design, materials and methods

We utilized the X Population Database (XPDB) which contains genealogic records of over 2.5 million individuals from original pioneers to current day inhabitants linked to a database containing the hospital and clinic diagnostic and procedural codes of 1.5 million people treated at X University since 1994. The relative risk of LUTS phenotypes in relatives of cases(grouped by ICD-9 or CPT-4 codes) were calculated by comparing the number of observed affected female relatives to the number expected, based on LUTS rates calculated internally from the XPDB. To confirm these findings, we also tested the hypothesis of excessive relatedness amont LUTS cases using the Genealogical Index of Familiality (GIF) statistic. While increased relative risks in close (first degree) relatives indicates a familial contribution (and thus, could be environmental and/or genetic), increased risks in second and third degree relatives strongly supports a genetic contribution.

Results

The first, second and third degree female relatives of women with different phenotypes of stress (SUI) and urge (UUI) urinary incontinence had significantly elevated relative risks of several LUTS phenotypes (table). However, only first degree relatives had an increased risk of nocturnal enuresis, primarily observed in individuals younger than age 20 years, suggesting common environmental, rather than genetic, influences. Nocturia demonstrated no evidence of either familial or genetic clustering. The excess relatedness (GIF) statistic confirmed the increased relative risks seen in family members.

Phenotype	N (cases)	95% CI for relative risk in relatives, degree: first	second	third	p value relatedness	familial/ genetic
SUI, all	1758	3.2*	1.6*	1.2*	<0.001	genetic
SUI, age ≤ 40	288	13.1*	0.0	3.3*	<0.001	genetic
SUI surgeries	240	7.9*	8.0*	1.1	<0.001	genetic
UUI	2186	2.9*	1.3*	1.2*	0.02	genetic
UUI, plus OAB**	3918	2.6*	1.4*	1.2*	<0.001	genetic
Total incontinence***	2316	3.1*	1.2*	1.3*	0.01	genetic
Nocturnal enuresis	944	13.6*	--	1.1	<0.001	familial
Nocturia	166	1.4	3.6*	0.3	0.31	neither

*p< .05
** includes any codes related to urge incontinence, urgency or frequency
***includes incontinence, not otherwise specified
-- there were no affected second degree relatives

Interpretation of results

The XPDB has been used to establish the familiality of other common conditions including breast cancer (1), aneurysm, and colon cancer. This model avoids the problem of ascertainment bias, and these findings support other reports of familial risk for UI (2). However, we found no evidence for a genetic contribution to nocturia or nocturnal enuresis, a condition previously reported to have a genetic contribution (3.)

Concluding message

There is evidence for a heritable contribution to multiple phenotypes of LUTS in women, suggesting that genes may be influencing these phenotypes. We have identified multiple high risk pedigrees for these phenotypes and will study them to identify genes predisposing to LUTS.

References

1. New Engl J Med (1988)31;533-7.
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