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Bladder neck mobility is a heritable trait

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Objective Congenital connective tissue dysfunction may partly be responsible for female pelvic organ prolapse and urinary incontinence. We undertook a heritability study to determine whether mobility of the bladder neck, one of the main determinants of stress urinary incontinence, is genetically influenced.

Design Heritability study using a twin model and structural equation modelling.

Setting Queensland Institute of Medical Research, Brisbane, Australia.

Population One hundred and seventy-eight nulliparous Caucasian female twins and their sisters (46 monozygotic pairs, 24 dizygotic pairs and 38 sisters) aged 18–24 years.

Methods We performed translabial ultrasound, supine and after bladder emptying, for pelvic organ mobility. Urethral rotation and bladder neck descent were calculated using the best of three effective Valsalva manoeuvres.

Main outcome measures Bladder and urethral mobility on Valsalva assessed by urethral rotation, vertical and oblique bladder neck descent.

Results Genetic modelling indicated that additive genes accounted for up to 59% of the variance for bladder neck descent. All remaining variance appeared due to environmental influences unique to the individual, including measurement error.

Conclusion A significant genetic contribution to the phenotype of bladder neck mobility appears likely.

INTRODUCTION

Urinary incontinence and prolapse of the pelvic organs are common complaints in women, leading to significant morbidity from the fourth decade of life onwards.[1] Directly or indirectly, they account for 10–30% of the workload of the gynaecological surgeon, and the lifetime risk of having to undergo anti-incontinence or prolapse surgery has been estimated at 11%.[2]

The main determinant of stress incontinence seems to be bladder neck descent (BND) on Valsalva,[3] and the relevance of organ mobility for the condition of pelvic organ prolapse is self-evident. It is likely that childbirth is the major environmental factor in the development of prolapse and stress incontinence,[4,5] and parturition seems to have a deleterious effect on pelvic organ support.[6] However, genetic factors probably also play a significant role, and the wide variation in this phenotype in young women suggests a genetic contribution.[7] Certain genetically determined connective tissue abnormalities (such as Marfan's and Ehlers Danlos syndromes) cause clinical conditions which are associated with skin, fascial and ligamentous relaxation as well as incontinence and prolapse,[8,9] and a family history of prolapse is a recognised risk factor.[10,11] Consequently, it seems reasonable to suspect a genetic contribution to the phenotype of bladder and urethral mobility.

In order to determine the need for population-genetic or molecular-genetic approaches, we undertook a study to define whether bladder and urethral mobility on Valsalva manoeuvre are a heritable trait.

METHODS

Caucasian females aged 18 to 24 years had initially been approached through mailouts to secondary schools in the Brisbane region to participate in genetic studies of melanocytic naevi and cognitive function. Zygosity was determined using a commercial kit and cross checked with blood group and other phenotypic data, giving an overall probability of correct assignment of greater than 99.99%.

All women gave informed written consent. They received a shopping voucher worth A$100 for their participation. Ethics Committee approval had been obtained from the local Ethics Committee (QIMR P434 (H0202-01-004)). In a detailed interview, we questioned bladder (stress and urge incontinence, frequency, nocturia, symptoms of voiding dysfunction and urinary tract infections) and bowel symptoms (straining at stool and chronic constipation), as well as a history of complaints associated with connective tissue dysfunction (dislocations, epistaxis and herniae), a history of bedwetting beyond school age and knowledge

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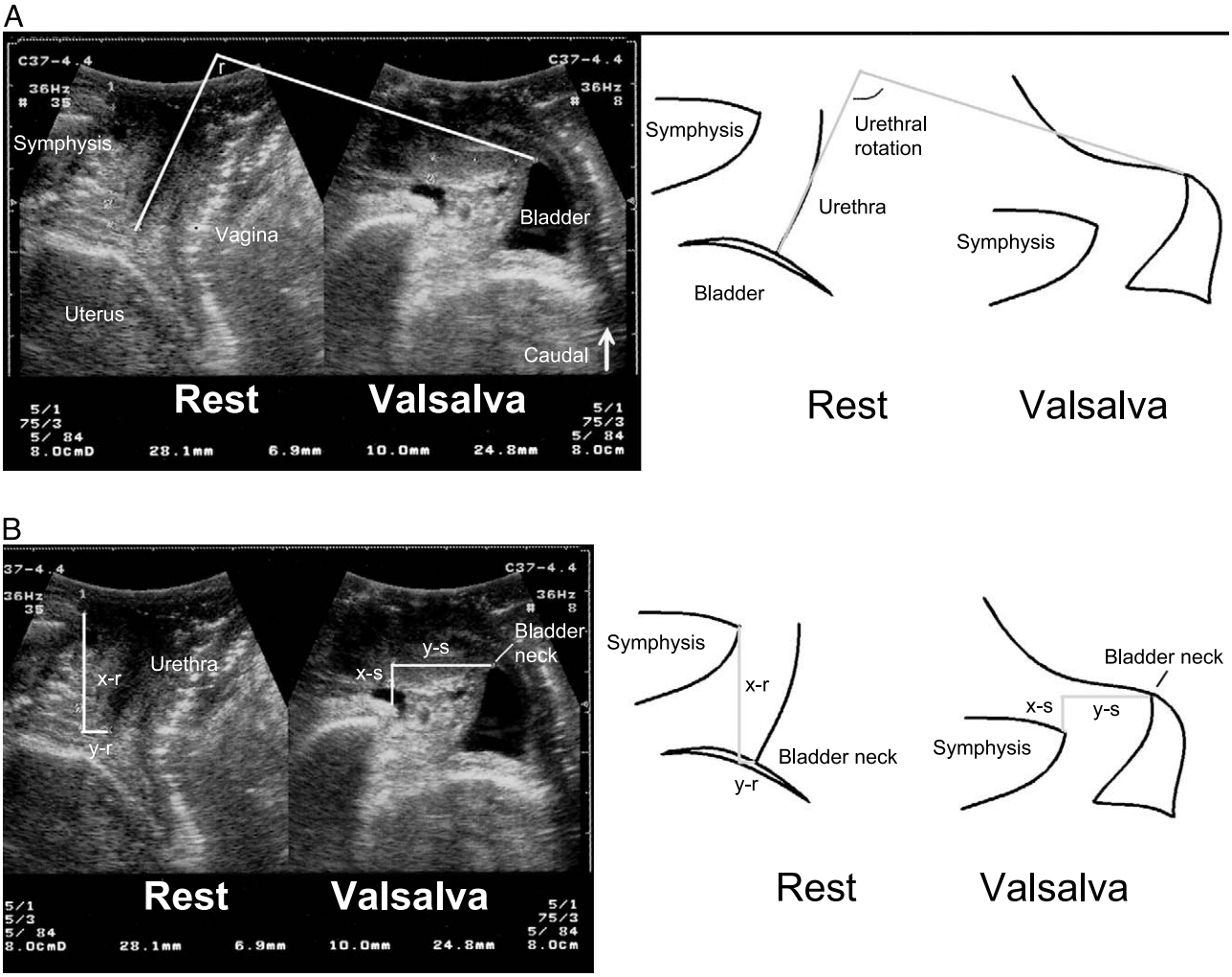

Fig. 1. (a) Translabial ultrasound (left) and line drawing (right) of the measurement of proximal urethral rotation on Valsalva. In this instance, urethtal rotation is 95°. (b) Translabial ultrasound (left) and line drawing (right) of the measurement of vertical and total (oblique) bladder neck descent on Valsalva manoeuvre, according to the formulae: vertical BND = $x\text{-}r - x\text{-}s$; OBND = SQRT($(x\text{-}r - x\text{-}s)^2 + (y\text{-}r - y\text{-}s)^2$).

and/or practice of pelvic floor muscle exercises. A family history of urinary incontinence, prolapse or surgery for these conditions was also elicited.

Study participants were examined by translabial ultrasound in order to quantify bladder and urethral mobility in a non-invasive fashion. Translabial ultrasound is increasingly used in urogynaecology,[12] has recently been shown to be highly reproducible[13] and to correlate well with clinical assessment.[14] Ultrasound was performed within 5 min after bladder emptying, supine and in the midsagittal plane. A more detailed description of the methodology used in the presented study has been published elsewhere.[12] For ultrasound imaging, we used Toshiba EcoCee and GE Kretz Voluson 730 systems with 3.5–7 MHz curved array transducers. All examinations were carried out under direct supervision of the first author or by personnel trained by him for at least 100 consecutive assessments.

Differences between measurements obtained at rest and on Valsalva manoeuvre were calculated as proximal urethral rotation, vertical BND and as oblique bladder neck descent (OBND) (see Figs 1a and 1b). The resulting measurements in Figs 1a and 1b are: urethral rotation, 95°; BND = 28.1 − 10.0 = 38.1 mm; OBND = SQRT [$(28.1 - 10.0)^2 + (6.9 - 24.8)^2$] = 42.1 mm. The bladder is invisible in the images at rest as it is completely empty.

At least three Valsalva manoeuvres were performed, with the most effective used for numerical evaluation. No attempt was made to standardise Valsalva strength as this would have required catheter placement. While a spirometric method of standardisation of Valsalva pressure has been described,[15] normal values obtained by this method appear unrealistically low,[16] and repeatability measures are currently unavailable. It is acknowledged that the absence of Valsalva standardisation introduces a confounding factor. However, the clinical importance of this is

likely to be limited as a test–retest series in a subpopulation of 50 women reassessed after a minimum of four weeks demonstrated excellent repeatability (intraclass correlation coefficient 0.77).[7]

Statistical analyses employed either SPSS or the software package Mx,[17] which used the method of maximum likelihood estimation from raw data observations[18] and which was used for all structural equation modelling. A basic assumption in twin studies is that means and variances are not influenced by the birth order of co-twins or by their zygosity. For example, the mean and variance for BND should be the same for a group of first-born twins from a monozygotic pair (MZ) and a group of second-born twins from a dizygotic (DZ) pair if the groups are large enough to be representative. These assumptions were tested by comparing a fully saturated model (i.e. means and variances were free to vary for both birth order and zygosity) to successively more constrained models in which means and then variances were firstly set equal for first- and second-born co-twins and secondly set equal for MZ and DZ pairs. When the constrained models do not differ significantly from the fully saturated model (by likelihood ratio tests), the assumptions are supported. In addition, means and variances for non-twin sisters were compared with those for twins, to show that the phenotypes were expressed similarly in both groups.

Means were further examined to determine whether the age of the individual was influencing the phenotypes. Both quadratic age effects (i.e. where the influence of age is not constant) and linear age effects (i.e. where the influence of age is constant) were tested by comparing models with and without constraints for age effects.

Twin correlations were computed for MZ and DZ pairs. In addition, DZ twin correlations were compared with those between non-twin sisters, and where the non-twin sister correlations could be set equal to the DZ twin correlations, the non-twin sister pairings were treated as DZ twin pairs. The twin correlations provide insights into the factors influencing individual differences in phenotypes, as MZ twins share 100% of their genetic material, but DZ pairs and non-twin sisters share on average only 50% of their genetic material. The influence of non-shared environment (E) only, or an E model, is indicated when the MZ correlation and the DZ correlation are both zero (i.e. $r_{MZ} = r_{DZ} = 0$). The influence of common environment (C) and non-shared environment (E), or a CE model, is indicated when $r_{MZ} = r_{DZ} > 0$. An AE model, indicating the influence of additive genes (A) and non-shared environment (E), is suggested when $r_{MZ} = 2\ r_{DZ} > 0$. The influence of additive genes (A), common environment (C) and non-shared environment (E), or an ACE model is indicated when $r_{MZ} < 2\ r_{DZ} > 0$. An ADE model indicates the influence of additive genes (A), dominant genes (D) and non-shared environment (E) and is suggested by $r_{MZ} > 2\ r_{DZ} > 0$.

The data for each variable were fitted to univariate models that allowed specific relationships between co-twins, which reflected their genetic inheritance. The correlation between the genetic factors (A and D) for MZ co-twins was fixed to 1.0. However, additive genes, in which paternal and maternal alleles are equally influential and dominant genes, in which the paternal or maternal allele is dominant, differentially influence DZ similarity. To reflect this, for DZ co-twins the correlation between A factors was fixed to 0.5, and between D factors to 0.25, as the influence of dominant genes reduces DZ co-twin similarity. The correlations between C factors for co-twins was 1.0 for both MZ and DZ pairs based on the assumption of comparable environments for MZ and DZ twins, which frequent empirical testing has on the whole supported,[19,20] and by definition, E factors were left uncorrelated for all pairs. Note that with a sample of twin pairs reared together, as in this study, D and C components are confounded and cannot be included in the same model[17] and a model containing the influence of dominant genes in the absence of additive genes (i.e. a DE model) is biologically implausible and is not considered.

All data were examined for normality of distribution and screened for univariate outlying individuals in SPSS. Univariate outlying families were identified using the %P option in Mx, which provided a likelihood statistic for each family conditional on the genetic model. Individual and family data were dropped if their z-score value was greater than ± 3 and the analyses rerun. Data lost due to outliers accounted for less than 3% of the data set.

RESULTS

One hundred and seventy-eight subjects were recruited: 46 MZ and 24 DZ twin pairs, and 38 non-twin sisters, producing a data set of 178 assessments. Table 1 lists history and symptoms. Of 178 women, two were completely unable to perform a Valsalva manoeuvre despite repeated efforts at teaching and were excluded from the analysis of ultrasound data.

Table 1. Personal history on 178 young nulligravid Caucasian females.

Personal history	*n*	%
Stress incontinence ≥1/month	14	8
Urge incontinence ≥1/month	12	7
Frequency	24	13
Nocturia	5	3
Knowledge of PFME	113	63
Conscious use of PFME	39	22
Constipation*	19	11
Straining at stool*	22	12
Dislocations	10	6
Nosebleeds	14	8
Herniae	1	1

PFME = pelvic floor muscle exercises.
* More than occasionally.

Table 2. Twin pair and non-twin sister correlations of ultrasound parameters of bladder neck mobility. Correlations (with 95% confidence intervals) are presented.

	Twin pair and non-twin sister correlations			Phenotypic correlations		
	r_{MZ} (44–46 pairs)	r_{DZ} (22–24 pairs)	Sister correlations (21–28 pairings)	BND	OBND	URot
BND	0.47 (0.23 to 0.65)	0.48 (0.07 to 0.71)	0.36 (−0.08 to 0.63)	1		
OBND	0.61 (0.40 to 0.75)	0.15 (−0.20 to 0.46)	0.25 (−0.25 to 0.55)	0.87	1	
URot	0.45 (0.21 to 0.63)	0.05 (−0.34 to 0.41)	0.12 (−0.35 to 0.49)	0.64	0.77	1

BND = bladder neck descent; OBND = oblique bladder neck descent; URot = urethral rotation.

On ultrasound, a wide range of values was obtained for all tested parameters. Proximal urethral rotation on Valsalva manoeuvre varied from 1° to 96° (mean 34°, SD 23.7), vertical BND was measured at 1.2 to 52.7 mm (mean 17.5, SD 9.1 mm) and OBND, signifying total bladder neck mobility on Valsalva, varied from 1.4 to 55.4 mm (mean 23.4, SD 10.3 mm). None of the parameters of bladder neck mobility correlated with personal or family history obtained in the interview. Vertical BND and OBND were near normally distributed and no transformations were required. A moderate positive skew was found for urethral rotation and this was corrected through square root transformation.

Among the twin pairs, no significant differences in means and variances were identified for either birth order or zygosity (i.e. $P > 0.05$ when comparing maximum likelihood estimates). In addition, all means and variances for siblings could be set equal to those of twins. There was a general trend for mobility to increase slightly with age in this sample. More specifically, quadratic age effects were found to be associated with OBND ($P = 0.01$) and urethral rotation ($P = 0.01$), such that descent and rotation decreased slightly between the ages of 17 and approximately 20 and then increased until the age of 25. The age effect was linear for BND ($P = 0.04$). Consequently, means were adjusted for the effects of age in all Mx modelling, including the comparisons of means.

Correlations were examined for MZ and DZ co-twins and for non-twin sister pairings (Table 2). The broad confidence intervals reflect a lack of power due to the small sample. However, genetic influence was indicated by lower DZ and/or non-twin sister correlations compared with MZ correlations (Fig. 2). The DZ correlations did not differ significantly from the non-twin sister correlations so these data were pooled, resulting in DZ/sister correlations of 0.42 (95% CI = 0.14 to 0.62) for BND, 0.18 (−0.10 to 0.44) for OBND and 0.07 (−0.22 to 0.37) for urethral rotation. Low DZ correlations for OBND and urethral rotation suggested the influence of dominant genes, but the confidence intervals indicated that these correlations could be much higher, and therefore the influence of common environment could not be ruled out. For BND, the MZ and DZ/sister correlations were similar, suggesting common environmental rather than genetic influence, but once again, the confidence intervals were broad, and close inspection of the data indicated that, to a large extent, the high DZ/sister correlation was due to the influence of only two pairs.

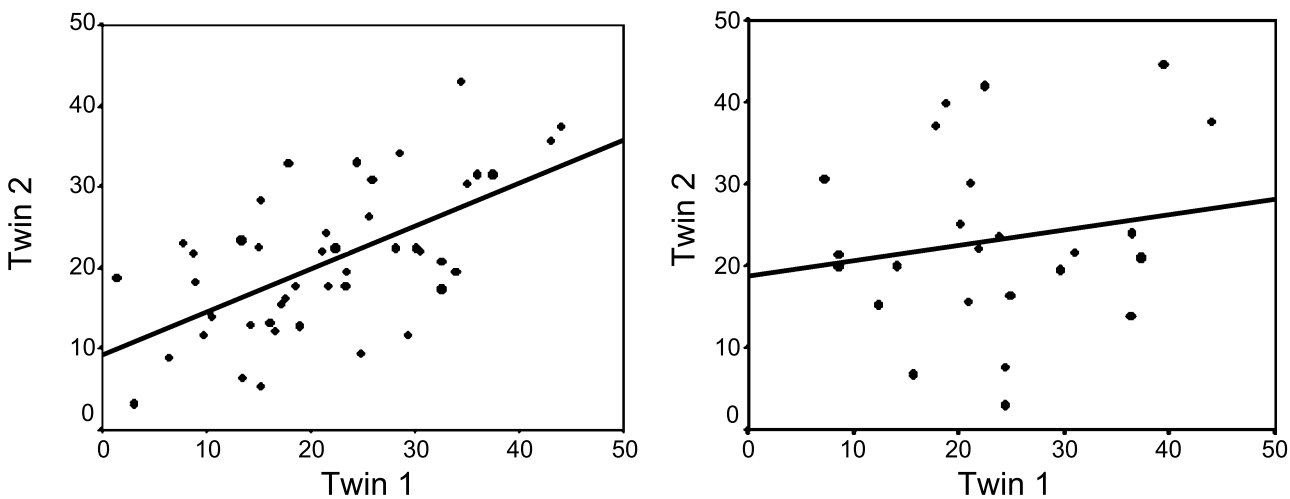

Fig. 2. Scatterplots showing greater twin similarity for MZ pairs (left-hand panel, $r = 0.61$) compared with DZ pairs (right-hand panel, $r = 0.15$) for OBND.

The twin and sister correlations suggested that either an ADE model [containing additive genetic (A), dominant genetic (D) and non-shared environmental (E) influences] or an ACE model [containing additive genetic (A), common environmental (C) and non-shared environmental (E) influences] may fit the data. Therefore, these fully saturated models were examined for each variable and compared with nested models (data not shown but available from author). For all variables, an E model was a worse fit to the data compared with the ADE and ACE models. The fit of AE models did not differ significantly from the fit of ADE models for any variable, indicating that a dominant genetic factor was not required to adequately explain the data and that AE models were the best fit to the data.

When compared with the fit of the ACE model, the CE model for OBND could be rejected as a worse fitting model and the AE accepted as the best fitting. For both BND and urethral rotation, both the AE and CE models appeared to be better fitting models than the ACE model. This indicated a lack of power to distinguish additive genetic and common environmental influences for these variables. However, both variables had high phenotypic correlations with OBND (0.87 for BND and 0.64 for urethral rotation), suggesting that sources of influence should be similar for all three variables and that, as for OBND, AE models may be more appropriate than CE models. Therefore, whether coming from an ADE or an ACE model, a model containing only additive genetic and non-shared environmental influences was found to be the best fit for OBND, and this pattern of influence was also considered likely for BND and urethral rotation.

Based on AE modelling for all variables, heritability estimates indicated that 59% (95% CI 38% to 74%) of the variance in OBND was due to the influence of additive genes, as was 51% (30% to 74%) of the variance in BND and 42% (18% to 61%) of the variance in urethral rotation. All remaining variance for these variables were influenced by non-shared environmental factors.

DISCUSSION

This study has demonstrated that bladder and urethral mobility in nulligravid women is partly determined genetically, with approximately 50% of variability due to genetic factors. This constitutes the first concrete evidence for the long-held hypothesis that genetic factors are partly accountable for pelvic floor morbidity such as incontinence and prolapse.

We excluded the most significant environmental influence on pelvic organ descent (i.e. childbirth), by studying only nulligravid individuals. Twin–twin correlations differed between MZ and DZ twins for most measures of bladder descent. This difference between MZ and DZ twin pairs was clear for OBND, but BND and urethral rotation did not show such clear evidence of genetic influence. However, while power was limited in this series, a genetic contribution to the phenotype of pelvic organ descent appears highly probable and subsequent multivariate analyses have indicated that genetic influence on the measures examined may be largely due to common genes.[21] Further population- and molecular-genetic work may be able to define the genes responsible for the marked phenotypic variation observed between individuals. Linkage studies, the next step in identifying responsible genes, will require a much larger number of phenotype assessments. It may therefore be some time before significant progress in this field will be reported.

What is the relevance of our findings for clinical practice? Firstly, the wide range of pelvic organ descent confirms previously reported findings in a smaller sample of the same study population.[7] It therefore appears that a significant minority of young women (20%) shows ultrasound evidence of first degree anterior, central or posterior compartment descent, and a smaller number seems to demonstrate second degree descent. Thus, our definitions of normality may require revision.

As regards a significant genetic contribution to bladder neck mobility and urethral rotation, the situation may be more complex than it appears. While BND on translabial ultrasound was associated with urodynamic stress incontinence in a mostly parous population,[3] the same parameter was not associated with subjective stress incontinence in the current series.[7] In pregnant women, BND has been identified as a risk factor for postpartum stress incontinence using a very different methodology.[15] It has not been possible to confirm this finding.[6] On the contrary, we and others have recently been able to show that high antenatal bladder neck mobility is associated with normal vaginal delivery.[22,23] If a mobile bladder neck is protective of operative delivery, then it may also protect against the associated morbidity of vaginal operative delivery or a long second stage (i.e. stress incontinence and prolapse).[24] On the other hand, this association between increased descent and normal delivery[22] has only been observed in pregnant women, and it may be explained by hormonal effects on pelvic connective tissue biomechanics, which alter the phenotype during pregnancy.[25]

Whether increased pelvic organ mobility in a young nulligravid patient is protective of or a risk factor for future pelvic floor morbidity, it is evident that prolapse observed in any individual may be congenital or genetic in origin, due to childbirth-related trauma, or the result of a combination of those factors. It stands to reason that such different aetiologies for pelvic organ hypermobility should have significant implications for treatment. It therefore seems imperative to improve our skills in assessing anatomy. As a result of recent developments in MRI and volume ultrasound techniques, the most promising approach for determining the aetiology of prolapse in a given patient may lie not with genetic but with imaging approaches.[12,26]

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