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The Heritability of Premenstrual Syndrome

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We aimed to determine (1) the prevalence of premenstrual syndrome in a sample of twins and (2) the relative contribution of genes and environment in premenstrual syndrome. A group of 193 subjects inclusive of same gender twins (n = 176) and females from opposite sex twin sets (n = 17) entered the study. Heritability analysis used same gender twin data only. The probandwise concordance rate for the presence or absence of premenstrual syndrome was calculated and the heritability of premenstrual syndrome was assessed by a quantitative genetic model fitting approach using MX software. The prevalence of premenstrual syndrome was 43.0% and 46.8% in monozygotic and dizygotic twins, respectively. The probandwise concordance for premenstrual syndrome was higher in monozygotic (0.81) than in dizygotic twins (0.67), indicating a strong genetic effect. Quantitative genetic modeling found that a model comprising of additive genetic (A) and unique environment (E) factors provided the best fit (A: 95%, E: 5%). No association was found between premenstrual symptom and the following variables: belonging to the opposite gender twin set, birth weight, being breast fed and vaccination. These results established a clear genetic influence in premenstrual syndrome.

■ **Keywords:** heritability, premenstrual, twin

Premenstrual syndrome, a common cyclic disorder of menstruating women, is defined by emotional and physical symptoms that constantly occur during the luteal phase (Dickerson, 2003). Estimates of the prevalence of premenstrual symptoms vary to a large extent, in part because of differences in questionnaire, definitions, and populations (Kendler, 1998). Many women experience no premenstrual symptoms, a substantial proportion experience mild symptoms, and a few women report severe or disabling symptoms. It is not known what the responsible factor for this variation is.

The family and twin studies of premenstrual symptoms published (Condon, 1993; Dalton, 1987; Glick, 1993; Kendler, 1992; Rubinow, 1984; van den Akker, 1987), with one exception (Glick, 1993), suggest that familial factors add significantly to individual differences in the susceptibility to premenstrual symptoms. However, of the four twin studies of premenstrual symptoms (Condon, 1993; Dalton, 1987; Kendler, 1992; van den Akker, 1987), only one, with 31 pairs, relied on prospective evaluation (Dalton, 1987). The three larger studies (Condon, 1993; Kendler, 1992; van den Akker, 1987) used single retrospective reports of premenstrual symptoms, the consistency and the legitimacy of which have both been questioned (Christensen, 1989; McFarland, 1989; Rubinow, 1984) and defended (Hart, 1987; Schilling, 1981). In twin studies using one time of measurement, the impact of genetic and environmental risk factors may be compounded by measurement bias. However, by using two measures, the importance of both genetic and environmental variation can be assessed with correction for fallibility of measurement (Kendler, 1992).

Materials and Methods

The data for this report come from a reproductive health study among Malaysian and Iranian twin pairs. A description of these twin registries is given elsewhere (Jahanfar, 2004). Zygosity was determined using a standard questionnaire (Eaves, 1989). We interviewed the twins through

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telephone after taking verbal consent. Information on both twins was taken during separate interviews. Female interviewers were chosen because participants were more willing to talk about issues related to menstruation. Interviewers were trained to ask for symptoms of premenstrual syndrome (PMS). Clinical symptoms of PMS asked were inclusive of physiological and psychological symptoms a week prior to menstrual flow such as abdominal cramps and breast tenderness. Presence of two or more symptoms was classified as 'yes' (presence of premenstrual syndrome) and those with just one symptom or no symptoms were classified as not having premenstrual syndrome (classified as 'no').

Ethical approval was obtained from the Medical Research Ethics Committee of University Putra Malaysia and Iran Avecina Research Center and registered with the National Malaysian Research Registry.

Statistical Analysis

All genetic analysis was carried out with MX, a software package specifically designed for the analysis of genetically informative data (Neale, 1997). Test of homogeneity showed no significant difference between the two countries.

Probandwise Concordance

Probandwise concordance was computed for MZ and DZ twin pairs from Tables 1 and 2 using the formula 2C/(2C+D), where C is the number of concordant twin pairs and D is the number of discordant twins pairs for PMS. (Millard et al., 2000). Heritability is indicated if the calculated value for MZ is higher than that of DZ twins.

Genetic Modeling

Two assumptions are involved when dealing with genetic modeling of environmental and genetic factors influencing a qualitative variable such as PMS. The first assumption is that there is a 'continuous underlying liability to disease' and secondly, that 'a threshold of liability' dichotomizes those with PMS from those without PMS. (Millard et al., 2000). Assuming that the underlying liability approximates a continuous bivariate normal distribution, tetrachoric correlation can then be estimated by the frequencies of concordant and discordant twin pairs from the two-by-two tables.

Contingent upon the assumptions being met, structural equation modeling was used to estimate the comparative genetic and/or environmental factors of the trait. This method has also been used by others (Millard, 2000). A linear structural model was then produced ($P = aA_i + dD_i + cC_i + eE_i$) where P is the probability of genetic or environmental effect of the trait, and all the elements on the right hand side of the formula are the variances of the uncorrelated latent factors with mean of zero and variance of one. The elements of the genetic component are inclusive of the additive component (A) and dominant component (D) while the elements of environmental factors are comprised of shared environment (C) and unshared environment (E). In order to relate these estimates to that of the population, the overall phenotype variance was then estimated by adding the square of variances for each estimate ($V_p = a^2 + d^2 + c^2 + e^2 = 1$) where V_p is the overall phenotype variance of the population (which adds up to 1) (Millard et al., 2000). The right hand side of the formula includes items a, d, c, and e, which are the regression coefficients of observed variables with the same components as the previous formula (a: additive genetic variance, d: dominant genetic variance and so on). These denote the strength of relationship between 'latent factors' and the phenotype under study (Snieder, 1997). For MZ twins, correlations between additive and dominant genetic factors between the twin 1 and twin 2 is one. For DZ twins, these values are 0.5 and 0.25, respectively. The tetrachoric correlation for MZ and DZ twins was then calculated by adding the genetic and environmental components as $r_{MZ} = a^2 + c^2 + d^2$ and $r_{DZ} = 1/2(a^2) + c^2 + 1/4(d^2)$ and heritability as $h^2 = a^2 + d^2$ (Millard et al., 2000).

In the current analysis, contingency tables were used to estimate the concordance of PMS for MZ and DZ. The maximum likelihood analysis method was used to fit these estimates (Neale, 1997). The significance of genetic factors was tested by comparing the complete model (with A, D, E and C) versus nested models (without the genetic component) using the Chi-square test. The same procedure was repeated for obtaining significance of environmental factors (comparing full model versus nested model with and without the environmental component, respectively). The best-fitting model was chosen by deducting the residual deviance of the compared models and by comparing Akaike's Information Criterion (AIC).

Results

One hundred and ninety-three female twins were recruited for the study inclusive of female–female twins ($n = 176$) and 17 females whose twins were males ($n = 17$). Same sex-twins were used for genetic analysis and they included 90 identical (45 pairs) and 58 (29 pairs) non-identical twins. Mean ($\pm$ *SD*) age of identical and non-identical twins were 29.91 $\pm$ 9.89 and 33.58 $\pm$ 8.83 respectively (range: 16–63 years). The prevalence of PMS was 43.0% in identical and 46.8% in DZ twins.

Concordance Analysis

Tables 1 and 2 show contingency tables of presence or absence of PMS for MZ and DZ twins, respectively. Thirty-eight out of 45 (84%) MZ pairs were concordant for PMS or no PMS, compared with 21 out of 29 (72%) DZ pairs. Probandwise concordance of PMS was 0.81 and 0.67 for MZ and DZ twins, respectively. The higher rate for MZ twins shows a genetic influence for PMS.

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Genetic Modeling

A strong genetic effect was found for PMS as the tetrachoric correlation for MZ twins (r_{mz}=0.96) was higher than for DZ twins (r_{dz} = 0.66) (Tables 1 and 2).

The result of model fitting to the data is shown in Table 3. Three nested models were compared with the full model as explained in the methodology section, investigating the effect of common and shared environment as well as the effect of genes on determination of PMS.

A significantly better fit was observed for all models with genetic component in comparison with the environmental model E and a relatively better fit compared with CE. Removing A (the genetic component) from the full model (ACE) and comparing the resulting nested model (CE) with the full model resulted in elevated χ^2 (from 2.132 to 5.084). This shows the influence of genetic factors in determining the PMS. When the full model was compared with the nested model without C (AE), χ^2 was found to be similar (2.132 and 2.781) suggesting a non-significant role of environmental factors on determination of PMS occurrence. Same results were found for comparing the ADE model with AE model. The largest χ^2 value belonged to the nested model with the environmental component E alone (χ^2 = 39.93; AIC = 29.93) showing the least fit to the data.

In summary, all the models with A component (ACE, ADE and AE) adequately fit to the data. The 'best fit' model, with the lowest AIC (-5.219), is the AE model. In other words, PMS variability could be best explained predominantly by the heritability component as the heritability variance in susceptibility to PMS was 95%. The remaining 5% variance was due to the effect of unique environmental component. The heritability (h^2) is 0.90.

Belonging to an opposite gender twin set did not make any difference in frequency of PMS when compared with same-gender twins (P = .159). There was no significant difference between the mean birth weight of twins with or without PMS (2346.67 ± 500 vs. 2337.50 ± 393 grams; p = .931). Being breast fed (p = .203) or vaccinated (p = .628) during childhood also did not show any relation with PMS.

TABLE 1

Contingency Table for Monozygotic Twins

Twin 1	Twin 2		
	No PMS	PMS	Total
No PMS	23	5	28
PMS	2	15	17
Total	25	20	45

Note: Probandwise concordance = $2 \times 15/((2 \times 15)+2+5)=0.81$. r_{MZ} = 0.96

TABLE 2

Contingency Table for Dizygotic Twins

Twin 1	Twin 2		
	No PMS	PMS	Total
No PMS	13	3	16
PMS	5	8	13
Total	18	11	29

Note: Probandwise concordance = $2 \times 8/((2 \times 8)+3+5) = 0.67$. r_{DZ} = 0.66

TABLE 3

Results From the Model for the Concordance Data

	a^2	c^2/d^2	e^2	χ^2	*df*	*P*	AIC
ACE	0.56	0.38	0.06	2.132	3	.545	-3.868
ADE	0.95	0.00	0.05	2.781	3	.427	-3.219
AE	0.95	0.00	0.05	2.781	4	.595	-5.219
CE	0.00	0.87	0.13	5.084	4	.279	-2.416
E	0.00	0.00	1.00	39.93	5	< .01	29.93

Note: a^2 = additive genetic variance; d^2 = dominant genetic variance; c^2 = common environmental variance; e^2 = unique environmental variance.

Discussion

Premenstrual syndrome is a common clinical entity with both physical and psychological symptoms. It is defined as cluster of symptoms (such as lower back and abdomen pain during menstruation, abdominal cramps, breast tenderness and anxiety women experience about a week prior to their menstruation). These symptoms are relieved by onset of menstrual flow and for some women are so severe that they can interfere with their life functions.

Genetic and environmental factors in premenstrual symptom reporting have been investigated previously through family and twin studies (Dalton, 1987; Glick, 1993; Kantero; 1971; Kendler, 1992; van den Akker, 1987). All of these studies have proposed a substantial heritable influence on PMS. Dalton (1987) reported greater resemblance for PMS among MZ twins in comparison with DZ twin pairs (95% vs. 44%) by examining 31 twin pairs. Condon (1993) examined 300 pairs of population-based Australian twins and found a correlation of 0.55 among MZ as opposed to 0.28 for DZ twin pairs. van dan Akker (1987) investigated PMS as assessed by self-report questionnaires in female twin pairs from two twin registries in UK (London and Birmingham) using 462 twin pairs. Familial aggregation of PMS was also investigated and heritability of 30% for London data and 80% for Birmingham samples were reported. Kendler (1992) reported a 35% estimation of heritability for 827 pairs of twins. Our results are also in harmony with the previous findings. The probandwise concordance rate for MZ twins in our study was 0.81 compared to 0.67 of DZ twins relating to the ratio of 1.21, which is suggestive of higher resemblance between MZ twins. Moreover, tetrachoric correlation for MZ twins was found to be higher than that of the DZ twins (0.96 vs. 0.66), which further emphasizes the heritability of this trait. Model fitting analysis found AE model as the best fitting model with the contribution of A (additive component of the genetic variance) to be

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95% and the contribution of non-shared environment to be only 5%.

All of the above mentioned studies, including that of ours, have been based on single retrospective reports of premenstrual symptoms and for that reason their validity have been questioned (Christensen, 1989; McFarland, 1989; Rubinow, 1984) and defended (Hart, 1987; Schilling, 1981). Kendler argues that retrospectively reported PMS symptoms are moderately stable over time, therefore attenuating the estimation of genetic and environmental contributions to the true or stable liability in PMS. The contribution of common environmental effect in the Kendler study (1998) was found to be zero and he believed that previous studies have been based on single reporting and did not take into consideration the measurement errors. He therefore rejects the idea that PMS is influenced by cultural, social or religious background or mother–daughter learning process as reported by Berry (1972). In any case, it is clear from our data and other studies that PMS has a strong heredity influence. Individual differences in reporting the symptoms might be due to personal perceptions of pain and discomfort. Our analysis failed to show any relation between birth weight, being breast fed or vaccination with PMS.

In conclusion, the quantitative genetic model fitting approach in twin sets provided a powerful means of examining the total genetic contribution in PMS and showed a major contribution of heredity (95%) in the variance of this trait.

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