Genetic Influences in Self-Reported Symptoms of Obstructive Sleep Apnoea and Restless Legs: A Twin Study

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Sleep disorders, such as obstructive sleep apnoea (OSA) and restless legs syndrome (RLS), are very common. The relative importance of genetic and non-genetic (environmental) influences on the symptomatology of these conditions has not been well studied. This study uses the twin design to examine this by evaluating OSA and RLS symptoms in monozygotic (MZ) and dizygotic (DZ) twins. Six thousand six hundred unselected female twin pairs, identified from a national volunteer twin register, were asked to complete a medical questionnaire. This questionnaire included questions on OSA and RLS symptoms, as well as questions on subject demographics, past medical history, smoking history and menopausal status. Responses were obtained from 4503 individuals (68% response rate). A total of 1937 twin pairs were evaluable: 933 MZ pairs (mean [range] age 51 [20–76] years) and 1004 DZ pairs (age 51 [20–80] years). Concordance rates were higher for MZ than DZ twins for OSA and RLS symptoms. Multifactorial liability threshold modeling suggests that additive genetic effects combined with unique environmental factors provide the best model for OSA and RLS symptoms. Heritability was estimated to be 52% (95% confidence interval 36% to 68%) for disruptive snoring, 48% (37% to 58%) for daytime sleepiness, 54% (44% to 63%) for restless legs, and 60% (51% to 69%) for legs jerking. These estimates dropped only slightly after adjustment for potential confounding influences on the symptoms of snoring and daytimble sleepiness. These results suggest a substantial genetic contribution to the symptomatology of OSA and RLS. More research is needed to identify the genes responsible, and may ultimately lead to new therapies.

Sleep disorders are very common and are becoming increasingly recognized. Obstructive sleep apnoea (OSA), defined by polysomnography, affects approximately 24% of men and 9% of women, aged 30 to 60 years (Bearpark et al., 1995; Young et al., 1993). OSA is associated with widespread comorbidity, including daytime sleepiness (Sforza & Kreiger, 1997), neurocognitive impairment (Engleman & Joffe, 1999), increased motor vehicle accidents (Young et al., 1997) and vascular disease (Peppard et al., 2000; Shahar et al., 2001). Restless legs syndrome (RLS), defined as an irresistible desire to move limbs, usually associated with paraesthesias/dysaesthesias and motor restlessness, is reported to be present in 5% to 15% of white adult populations (Odin et al., 2002).

Several papers have addressed acquired risk factors for these disorders, such as obesity and cigarette smoking for OSA patients (Lindberg, 1998; McNamara et al., 1993; Redline & Strohl, 1998), and iron deficiency, neuropathy and renal failure for RLS patients (Callaghan, 1966; Roger et al., 1991; Salvi et al., 1990). Family history also appears to play an important part in symptomatology for both of these conditions (Gislason et al., 2002; Guilleminault et al., 1995; International Restless Legs Syndrome Study Group, 1995; Manon-Espaillat et al., 1988; Mathur & Douglas, 1995; Ondo & Jankovic, 1996; Redline et al., 1992; Strohl et al., 1978; Wittig et al., 1988). However, there have been few large genetic studies of OSA and RLS patients, especially using the twin methodology to determine heritability.

Studies of monozygotic (MZ) and dizygotic (DZ) twins give important insights into the relative contributions of genetic and environmental factors to a trait. This study uses the twin design to determine the extent to which individual differences in reports of symptoms of obstructive sleep apnoea and restless legs are due to genetic or nongenetic (environmental) influences.

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Method

Subjects

The study subjects comprised female–female twin pairs recruited from the St Thomas' UK Adult Twin Registry (Spector & Macgregor, 2002; St Thomas' Adult UK Twin Registry, 1998). These subjects were originally recruited through a national media campaign and from twin registers (Spector et al., 1996) and were unaware of any particular hypotheses being tested. Zygosity was determined by a standard questionnaire and by genotyping in cases of uncertainty (Martin & Martin, 1975). Our institutional ethics committee approved the study, and all the women gave informed consent.

Questionnaire

Each subject was surveyed about symptoms of OSA and restless legs. Questions were also asked about demographics, past medical history, smoking history and menopausal status. These questions formed part of a larger postal self-administered questionnaire. Other data from this questionnaire have been published elsewhere (Hakim et al., 2002; Hakim et al., 2003; Mohammed et al., 2003).

Questions regarding two cardinal symptoms of OSA were included in the questionnaire. Subjects were asked about whether they 'ever' snored, and if so, how often their snoring disturbed others or caused them to wake up. Subjects were then asked how often, if at all, they experience sleepiness during the daytime. Answers to the latter two frequency questions could be any of the following: 'never', 'rarely', 'sometimes', 'frequently' or 'always'.

Subjects were surveyed for restless leg symptoms using two questions, one asking whether the subjects 'ever experience an urge to move (their) legs during the night to relieve tingling or numbness' and the other asking whether subjects 'ever find (their) legs jerk involuntarily during the night'.

Genetic Modeling

Quantitative genetic model fitting — based on comparison of the covariance (or correlation) of the disorder between MZ and DZ twins (Neale & Cardon, 1992; Sneider et al., 1997) — allows separation of the observed phenotypic variance into additive (A) and dominant (D) genetic components and into common (C) and unique (E) environmental components. The maximum likelihood modeling method used in twin analysis of dichotomous traits assumes that variation in the underlying liability of the disorder is normally distributed (Neale & Cardon, 1992). The correlation in liability among twins can be estimated from the frequencies of disease-concordant and disease-discordant pairs using a mulitifactorial liability threshold model (Falconer, 1989; Neale & Cardon, 1992; Sham et al., 1994). The significance of additive genetic factors, the common environment, and dominant genetic factors as components of the variance is assessed by removing each in submodels and testing the deterioration in fit compared with the full model.

Table 1

Demographic Details of the Twins Studied

	Monozygotic twins (n = 1866)	Dizygotic twins (n = 2008)	p value
Age (y)	51 (20–76) *	51 (20–80) *	0.59
Body mass index (kg/m2)	24.8 (13–52) *	25.1 (14–47) *	0.03
Hypertension[1]	18%	19%	0.58
NIDDM[2]	1%	1%	0.89
Current smokers[3]	15%	18%	0.01
Ever smoked[3]	42%	48%	0.00
Premenopausal[4]	41%	41%	0.88
Postmenopausal[4]	43%	41%	0.25

Note: p values are corrected for relatedness of the twins.
*mean (range).
[1] Hypertension: 'Have you ever been diagnosed by a doctor as having suffered from high blood pressure (not during pregnancy)?' (responses = yes or no)
[2] NIDDM = noninsulin dependent diabetes mellitus: ' Have you ever been diagnosed by a doctor as having suffered from diabetes (noninsulin dependent adult onset)?' (responses = yes or no)
[3] Smoking: 'Have you ever smoked cigarettes, cigars or a pipe on a regular basis?' (responses = never; yes & current smoker; yes but ex-smoker)
[4] Menopause: 'What is your menopausal status (responses = premenopausal; going through menopause now; postmenopausal, don't know)?'

Statistical Analysis

Demographic differences between MZ and DZ twins were compared using generalised estimating equations, which correct for relatedness of the twins in a pair. The difference in concordance rates between MZ and DZ twins was compared using the χ^2 test. Logistic regression analysis was used to assess the independent contribution of potentially confounding variables (BMI, smoking history, menopausal and snoring status) to the dependent variables for snoring and daytime sleepiness. In the genetic modeling, submodels were compared with the full model by

Table 2

Prevalence of Symptoms of Obstructive Sleep Apnoea and Restless Leg Syndrome

	Monozygotic twins (n = 1866)	Dizygotic twins (n = 2008)	p value
Ever snore	69%	72%	0.10
Disruptive snorer[1]	6%	6%	1.00
Daytime sleepiness[2]	21%	22%	0.48
Restless legs	39%	36%	0.09
Legs jerk	48%	45%	0.06

Note: [1] Defined as snoring that disturbed others or caused them to wake up ' frequently' or 'always'.
[2] Defined as experiencing sleepiness during the daytime 'frequently' or 'always'.

Table 3

Concordance Rates for Disruptive Snoring, Daytime Sleepiness and RLS Symptoms in Monozygotic and Dizygotic Twins

Characteristic	Twin type	Total pairs	Discordant pairs	Concordant pairs	Casewise concordance rate*	Risk ratio
Disruptive snorer	MZ	889	78	15	28 (17–39)%	2.0 ($p = .06$)
	DZ	949	98	8	14 (5–23)%	
Daytime sleepiness	MZ	912	223	83	43 (37–49)%	1.3 ($p = .03$)
	DZ	991	298	74	33 (28–39)%	
Restless legs	MZ	911	278	215	61 (56–65)%	1.4 ($p < .001$)
	DZ	983	390	159	45 (40–49)%	
Legs jerk	MZ	912	274	300	69 (65–72)%	1.3 ($p < .001$)
	DZ	977	296	236	54 (50–58)%	

Note: *95% confidence intervals in parentheses.

hierarchic χ^2 tests and the significance of change in the χ^2 goodness-of-fit statistic was assessed. Data handling, preliminary analyses, and genetic modeling were performed using STATA (StataCorp, 1997).

Results

Three thousand three hundred twin pairs (n = 6600) were surveyed. Of these, 4503 individuals returned a completed questionnaire (68% response rate). Singletons were dropped for the analyses, giving 3874 respondents who paired up; 933 MZ pairs (n = 1866) and 1004 DZ pairs (n = 2008). There were no differences in response rates between MZ and DZ groups (Hakim et al., 2002). The demographic details of the two groups are shown in Table 1. The two groups were well-matched for age, hypertension, Noninsulin Dependent Diabetes Mellitus (NIDDM) and menopausal status. DZ twins had a higher Body Mass Index (BMI) and were more likely to be current smokers or to have ever smoked. However, these later differences, although statistically significant, were small.

Table 2 shows that the prevalence of symptoms of OSA and restless legs in the two groups of twins was not statistically different.

The concordance rates and risk ratios for disruptive snoring, daytime sleepiness and restless legs symptoms are shown in Table 3. Casewise concordance rates were higher in MZ than DZ twins for all the variables studied. The risk ratios suggest that MZ co-twins are approximately one and a half times more likely to suffer from daytime sleepiness (risk ratio 1.3, $p = .03$), restless legs (risk ratio 1.4, $p < .001$) and legs jerking (risk ratio 1.3, $p < .001$) if their co-twin has the symptom compared with DZ co-twins. A difference in concordance between the twin pairs was also present for the symptom of disruptive snoring, though the risk ratio did not quite meet statistical significance (risk ratio = 2.0, p =.06). This was probably due to the low numbers of concordant pairs for this symptom.

The results of logistic regression analyses for potential risk factors for snoring and daytime sleepiness expressed as odds ratios are shown in Table 4. Increasing BMI and a smoking history (now or ever) independently increased the odds of reporting snoring (disruptive or ever) and daytime sleepiness. Premenopausal status significantly reduced the odds of snoring (disruptive or ever), while postmenopausal status significantly increased the odds of ever snoring, but not disruptive snoring. Snoring (disruptive or ever) significantly increased the odds of reporting daytime sleepiness.

The results of the genetic modeling analysis are shown in Table 5. Model fitting revealed that the effects of the shared environment of the twins (C) and the dominant genetic effect (D) could be dropped from the model without significantly worsening the χ^2 goodness-of-fit statistic. However, additive genetic effects (A) could not be eliminated. A model containing only parameters for additive genetic factors (A)

Table 4

Logistic Regression Analyses of Potential Risk Factors for Sleep Disorders Symptoms

Characteristic	Variable	Odds ratio (95% CI)	p value
Ever snore	BMI	1.13 (1.10–1.15)	$p < .001$
	Ever smoke	1.45 (1.27–1.66)	$p < .001$
	Now smoke	1.40 (1.17–1.69)	$p < .001$
	Premenopausal	0.59 (0.51–0.68)	$p < .001$
	Postmenopausal	1.40 (1.21–1.62)	$p < .001$
Disruptive snorer	BMI	1.12 (1.10–1.14)	$p < .001$
	Ever smoke	1.46 (1.13–1.87)	$p = .003$
	Now smoke	1.49 (1.10–2.01)	$p = .009$
	Premenopausal	0.52 (0.39–0.71)	$p < .001$
	Postmenopausal	1.31(0.99–1.73)	$p = .057$
Daytime sleepiness	BMI	1.03 (1.02–1.05)	$p < .001$
	Ever smoke	1.28 (1.11–1.47)	$p = .001$
	Now smoke	1.53 (1.30–1.82)	$p < .001$
	Ever snore	1.46 (1.24–1.72)	$p < .001$
	Disruptive snorer	2.18 (1.68–2.82)	$p < .001$

Table 5

Genetic Modeling Analyses for Sleep Disorders Symptoms

Symptom	Model	A (95% CI)	C/D (95% CI)	Difference in $\chi 2$	*p* value*
Disruptive snorer	ACE	0.52 (–0.01–1.05)	0.00 (–0.44–0.44)	–	–
	CE	–	0.40 (0.27–0.53)	7.65	0.00
	AE	**0.52 (0.36–0.68)**	**–**	**0.00**	**0.99**
	ADE	0.52 (–0.30–1.35)	-0.00 (–0.88–0.88)	–	–
Daytime sleepiness	ACE	0.46 (0.13–0.78)	0.02 (–0.24–0.27)	–	–
	CE	–	0.35 (0.27–0.43)	15.14	< 0.001
	AE	**0.48 (0.37–0.58)**	**–**	**0.04**	**0.85**
	ADE	0.51 (0.04–0.97)	–0.03 (–0.54–0.47)	–	–
Restless legs	ACE	0.69 (0.40–0.98)	–0.13 (–0.35–0.10)	–	–
	CE	–	0.39 (0.31–0.46)	44.44	0.00
	AE	**0.54 (0.44–0.63)**	**–**	**2.46**	**0.12**
	ADE	0.31 (–0.10–0.72)	0.25 (–0.19–0.70)	–	–
Legs jerk	ACE	0.70 (0.42–0.99)	–0.09 (–0.30–0.13)	–	–
	CE	–	0.43 (0.36–0.50)	48.46	0.00
	AE	**0.60 (0.51–0.69)**	**–**	**1.13**	**0.29**
	ADE	0.46 (0.06–0.85)	0.17 (–0.27–0.60)	–	–

Note: A = additive genetic; D = dominant genetic; C = common environment; E = unique environment.
* Compared with ACE model.
Best fitting model in bold.

and the unique environment of the twins (E) best explained the variance in liability for all the symptoms examined within this population.

Heritability for disruptive snoring, daytime sleepiness, restless legs and legs jerking was estimated to be 52% (95% confidence interval 36% to 68%), 48% (37% to 58%), 54% (44% to 63%), and 60% (51% to 69%) respectively. Thus, approximately half of the variance in liability to these symptoms is due to genetic factors.

Following adjustment for potentially confounding factors (Table 4), the proportion of phenotypic variance accounted for by genetic factors was reduced to 42% (95% confidence interval 23% to 61%) and 45% (33% to 57%) for disruptive snoring and daytime sleepiness respectively.

Discussion

This study has shown a clear genetic influence on snoring, daytime sleepiness, restless legs and leg jerking in female twins. Genetic modeling in this study suggests that approximately half of the variation in liability for these symptoms is due to genetic factors. Further, these estimates dropped only slightly after adjustment for confounding influences on the symptoms of snoring and daytime sleepiness, which are themselves (like BMI and smoking) also partly under genetic influence.

Previous studies have examined the heritability of OSA and its symptoms. Early studies described the occurrence of OSA in multiple members of selected families (Manon-Espaillat et al., 1988; Strohl et al., 1978; Wittig et al., 1988). Following this, Redline and co-workers (1992) reported that first-degree relatives of index probands with proven sleep apnoea were two to three times more likely to report symptoms of disturbed sleep (breathing pauses and excessive daytime sleepiness respectively) than were first-degree relatives of control probands. A progressive increase in risk for reporting these symptoms was associated with increasing numbers of relatives reporting the same symptom, further suggesting an important familial basis for sleep-related breathing disturbances. More recent studies further support the familial aggregation of OSA symptoms (Gislason et al., 2002; Guilleminault et al., 1995; Mathur & Douglas, 1995).

Family studies are limited in that they cannot separate common environment from genetic factors. Twin studies give further insights into the heritability of diseases or their symptoms. Three twin studies have examined the genetic basis for snoring and daytime sleepiness (Carmelli et al., 2001; Ferini-Strambi et al., 1995; Kaprio et al., 1988). Kaprio et al. (1988) and Ferini-Strambi et al. (1995) have both reported a higher concordance for snoring among MZ twins than among DZ twins, suggesting a role for inheritance in snoring. Most recently, Carmelli et al. (2001) estimated that genetic factors accounted for 23% of the variability in snoring and 40% of the variance in daytime sleepiness as ascertained by self-reporting via questionnaire in their sample of 1600 male–male twin pairs. The study results complement these, showing heritability estimates of 42% and 45% for disruptive snoring and daytime sleepiness, respectively, from a larger twin

cohort (n = 3874) of female–female twin pairs. Importantly, the higher heritability estimate for snoring in female–female twin pairs raises the possibility that genetic factors are more important in women for this symptom than in men. An important strength of the study is that the estimates have corrected for possible confounding influences on the symptoms of snoring (BMI, smoking and menopausal history) and daytime sleepiness (BMI, smoking and snoring history).

Restless legs syndrome is generally segregated into primary (idiopathic) and secondary (related to known causes such as uraemia, peripheral neuropathy and iron deficiency anaemia) forms. In at least 60% of primary RLS cases, a family history is reported by the patient (International Restless Legs Syndrome Study Group, 1995; Ondo et al., 1996). No studies to date have applied quantitative genetic model fitting to a large sample of twins as we have in this study, to document this heritability in more detail. Using this methodology, just over half of the variation in liability to the symptoms of restless legs and legs jerking was found to be due to genetic factors.

Although the data from this study are consistent with multiple genetic effects contributing to restless legs symptoms, other studies have suggested an autosomal dominant pattern of inheritance (Bonati et al., 2003; Winkelmann et al., 2002). Further, a locus mapping to chromosome 14q in a family with an autosomal dominant inheritance pattern has been identified (Bonati et al., 2003). However, another potential susceptibility locus for RLS has been mapped to chromosome 12q, with this study suggesting an autosomal recessive mode of inheritance (Desautels et al., 2001). Given the discrepancies, more work is clearly needed now to clarify the exact mode of transmission and the responsible genes — although most common traits show additive or polygenic inheritance and there is considerable scope for error in segregation studies.

Criteria for the diagnosis of restless legs syndrome have been developed by consensus approach (International Restless Legs Syndrome Study Group, 1995). A shortcoming of this study is that these criteria were not used to diagnose restless legs syndrome. It is likely that this has led to some misdiagnosis of this condition, which may explain the high prevalence figures in this study. However, studies addressing RLS will always be flawed by the inherent problems associated with a diagnosis based on self-report of symptoms, since there is no objective gold standard for diagnosing this condition. This study did not separate restless legs syndrome into primary or secondary forms. Potentially causative factors for RLS symptoms, such as low serum ferritin levels, were not measured in this study. If the secondary RLS cases could have been removed from the analyses, the heritability estimates may have been even higher, as has been reported previously (Ondo et al., 1996).

An important consideration in the interpretation of the findings from this work is whether the twins are truly representative of the general population. Selection bias is unlikely to be a significant problem in this study because the large postal questionnaire did not focus on a particular disease and all the twin pairs recruited were unselected volunteers. Our twin population has also been found to be similar to a population-based singleton sample for a number of common medical conditions and lifestyle characteristics (Andrew et al., 2001). Other studies that have examined women of similar age to those in this study have reported a comparable prevalence for snoring (Netzer et al., 2003; Ohayon et al., 1997), disruptive snoring (Larsson et al., 2003) and daytime sleepiness (Netzer et al., 2003). However, it is difficult to compare directly between these studies and ours, as the wording of the questions used is different. A similar problem exists when comparing the prevalence of RLS symptoms between this study and others.

The results of this study may not be directly applicable to males as the twin population examined was only female. This is especially the case for those results concerning the symptoms of OSA, as there are clear gender differences in the prevalence of OSA and its symptoms (Larsson et al., 2003; Young et al., 1993). Our twin population has a female bias for historical reasons, as the rheumatological conditions initially examined are more common in women (Mohammed et al., 2003).

In conclusion, in the present study we have shown that MZ female twins are more likely to be concordant for symptoms of OSA and RLS than DZ female twins. These results indicate a substantial genetic contribution to the etiology of these disorders. Genetic modeling suggests that approximately half of the variation in liability to these symptoms is due to genetic factors. This research highlights the importance of genetic influences in symptomatology, extends previous work in this area, and suggests the need for more research for the responsible genes which may ultimately lead to new therapies.

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