



GENESiS: creating a composite index of the vulnerability to anxiety and depression in a community-based sample of siblings

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There is considerable evidence for a unitary and dimensional view of the genetic vulnerability to symptoms of anxiety and depression. The GENESiS (Genetic Environmental–Nature of Emotional States in Siblings) Study aims to use a multivariate approach to detect genetic loci that contribute to individual differences in this vulnerability dimension. The study used the UK General Practice Research Framework to generate a community-based sample of siblings. Questionnaire measures of anxiety/depression included the short form of the neuroticism scale from the revised Eysenck Personality Questionnaire (EPQ-N), the General Health Questionnaire (GHQ-12), and the anxious arousal and high positive affect subscales from the Mood and Anxiety Symptoms Questionnaire (MASQ-AA and MASQ-HPA). Genetic model-fitting of 2658 unselected sibships provided evidence for a single common genetic (familial) factor that accounted for a substantial proportion of the genetic variances and covariances of these four measures. Using the parameter estimates of this model, we constructed a composite index of this common genetic factor. This index, which has a sib correlation of 0.22, will be used as a quantitative phenotype in the molecular genetic phase of GENESiS. *Twin Research* (2000) 3, 316–322.

Keywords: depression, anxiety, neuroticism, sibships, genetics, vulnerability

Introduction

There is substantial evidence from epidemiological and genetic studies for a single dimension of genetic vulnerability to anxiety and depression.^{1–3} Numerous studies have documented a substantially greater degree of co-morbidity than expected by chance between the two disorders.^{4–9} For example, in the Zurich study conducted by Angst and Dobler-Mikola⁴ the 1-year prevalence rate of major depression co-occurring with anxiety was 36%, while for the population sample as a whole, the prevalence rate for major depression was only 7.0%. The two disorders also have a similar profile of epidemiological risk factors; Eaton and Ritter⁵ used a psychiatric diagnostic interview to devise an index for anxiety and an index for depression, and found these two indices to have very similar ‘sociodemographic fingerprints’.

Goldberg et al⁶ examined the symptoms shared by common psychiatric disorders in a primary care setting. One of their core assumptions was that common psychiatric disorders would fit a dimensional rather than a categorical diagnostic model.^{10,11} They factor-analysed the 28-item General Health Questionnaire and interview items from the Psychiatric Assessment Schedule, and found two highly correlated ($r = 0.7$) factors that represented anxiety and depression dimensions. This suggested a single major dimension of symptoms that accounted for 70% of the variance of both anxiety and depression, and a second dimension that explained the remaining 30% of the variance of symptoms that are more specific to anxiety or depression. They speculated that the major dimension reflected a biological vulnerability to psychiatric disorder, while the secondary dimension was indicative of environmental influences.

The hypothesis that there is a shared genetic vulnerability to anxiety and depression has been supported by extensive quantitative genetic research.^{1,2,12–15} For example, in a study of nearly 4000 twin pairs, Kendler et al¹³ showed that genes acted in a non-specific fashion to influence the general level of symptoms of anxiety and depression.

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Similarly, in another study of 1030 female twin pairs, Kendler *et al*¹⁵ showed that genetic influences on phobias, panic disorder, bulimia nervosa, generalised anxiety disorders, major depression, and alcoholism fell into two factors. The first loaded heavily on phobia, panic disorder, and bulimia nervosa; the second loaded on to major depression and generalised anxiety disorder; the genetic vulnerability to alcoholism was largely independent of both factors. These results offer strong support for a single genetic dimension in the vulnerability to anxiety and depression.

There is evidence to suggest that the general vulnerability to anxiety and depression may be indexed by the personality scale of neuroticism.¹⁶ Jardine *et al*¹⁷ showed in a study of 3810 Australian twin pairs that variations in symptoms of anxiety and depression were largely dependent on the same factors as those that determined neuroticism. Similarly, in the Virginia twin sample, neuroticism was found to be strongly predictive of an onset of major depression in a one-year period.¹⁸ Furthermore, genetic factors accounted for approximately 70% of the correlation between neuroticism and major depression.

The evidence reviewed above supports a dimensional and unitary view of the vulnerability to anxiety and depression. The goal of the GENESiS (Genetic Environmental-Nature of Emotional States in Siblings) Study is to apply quantitative genetic methodology to a large community-based sample of sibling pairs in order to identify quantitative trait loci (QTL) for a general dimension of vulnerability to anxiety and depression. Although there is evidence that neuroticism is an index of this vulnerability, no study has addressed this issue using siblings. Therefore, GENESiS adopts an empirical, multivariate approach for the measurement of this latent variable. In addition to neuroticism, we also include three other scales that measure general mental health, autonomic anxiety and mood. Our hypothesis is that quantitative genetic modelling of these four measures will confirm a single underlying genetic (familial) vulnerability. This would allow the construction of a single composite index of the genetic vulnerability to anxiety and depression that would be optimal for future molecular genetic studies.

Methods

Subjects

The GENESiS study is based in the United Kingdom. Subjects were recruited through the Medical Research Council's General Practice Research Framework (GPRF). The GPRF was set up more than 20 years ago to enable high quality data to be

collected on large-scale community samples. The GPRF now comprise more than 1000 large practices distributed throughout the United Kingdom.

The participating GPs identified the names and addresses of all patients on their registers aged between 20 and 55 years, excluding those with severe learning disabilities or psychotic illness. We also suggested that those patients who were particularly vulnerable (eg with terminal illnesses) be excluded, although this was left to the GP's discretion. An initial notification letter was sent to the subjects to inform them that their GP practice was involved in a new study about depression and anxiety, and that they would be sent a questionnaire (see Eaker *et al*¹⁹ or Etter *et al*²⁰ for more information on the benefits of notification letters in mailing surveys). The subjects were able to opt-out of the study by calling a freephone number or contacting the GP. In the second mailing, a questionnaire (called the index sibling questionnaire) was sent together with an introduction letter from the GP. Four weeks after the questionnaire was mailed, a general reminder letter was sent to all subjects. Finally, a further questionnaire was sent to the non-responders four weeks after the general reminder letter. From the returned index sibling questionnaires we generated a mailing list for non-index siblings. A questionnaire was mailed to non-index siblings approximately one month after the study received the original index sibling questionnaire. A second questionnaire was mailed to the non-responders among the non-index siblings 8 weeks after the first mailing.

In this report, we present an analysis of data collected up to March 1999. By this date, 10 GP practices across England had participated in the study. The GPs reflect the full range of rural and urban practices in the UK. The participating GP practices generated a list of 51 806 people. In total, the GPs requested that 421 people be taken out of the mailing list, representing 0.008% of the overall total. A further 1799 questionnaires were returned due to incorrect addresses (3.5% of the total). This left a maximum of 49 586 index subjects who were actually contacted.

Measures

The questionnaires to both index subjects and non-index siblings included several well-validated and standardised instruments for the measurement of anxiety/depression related traits, other personality traits, and psycho-social adversity. The General Health Questionnaire (12-item version; GHQ12) was used as a test of general mental health symptoms.²¹ The short form of the neuroticism scale from the revised Eysenck Personality Questionnaire (EPQ-N)

was used as a measure of trait anxiety.²² Short forms of two subscales were used from the Mood and Anxiety Symptoms Questionnaire²³ to measure level of anxious arousal (MASQ-AA) as well as high positive affect (MASQ-HPA). Other measures such as life events and social problems were also included for future analyses of interactions with anxiety and depression.

Statistical analyses

Structural equation models were fitted to the sibship data on the four measures: GHQ12, EPQ-N, MASQ-AA and MASQ-HPA. When used on twin data under the equal environment assumption, structural equation models are able to partition phenotypic variance into components due to genes, environmental factors shared by siblings, and environmental factors unique to the individual. The current study, which employs a sibship design for the purpose of subsequent linkage and association analysis, cannot discriminate between genetic and shared environmental influences. Nevertheless, there is a substantial literature of studies on adult twins that supports the importance of genetic influences and the lack of important shared environmental influences.^{14,24} We have therefore omitted shared environmental influences from our models. We emphasise that, because of this necessary omission, the 'genetic' effects estimated from our analyses are really familial effects that may contain environmental influences shared by siblings.

Estimates of within-sib/cross-traits correlations were obtained from the entire sample of subjects who returned questionnaires, including those without siblings. Estimates of between-sibs/same-traits correlations, and between-sibs/cross-traits correlations were obtained by doubly entering all possible sibling pairs in sibships of size 2 and 3. Structural equation models were fitted by maximising the log-likelihood function of the raw sibship data on the four standardised (mean 0, variance 1) measures, pre-adjusted for age and sex, using the Mx software.²⁵ After fitting a saturated model where all means, variances and covariances were free parameters, we proceeded to fit a model with a Cholesky decomposition of the additive genetic effects, and a Cholesky decomposition of non-shared environmental effects. Three further restricted models were examined. The first restricted model replaced the Cholesky genetic factors by a single common genetic factor and four specific genetic factors. We call this the common genetic factor model (see Figure 1). The second replaced the Cholesky environmental factors with a single common environmental factor and four specific environmental factors. We call this the common environmental factor model. The final

restricted model was obtained by replacing both Cholesky genetic and environmental factors by common and specific genetic and environmental factors. This is the standard common factor, independent pathways model.²⁶

Results

Response rates and sociodemographic characteristics

The total number of fully completed returned questionnaires for index siblings is 22 087 (response rate 45%). We also asked people who did not want to take part in the study to return the forms and to complete four demographic measures that included: current employment, level of education, ethnicity, and type of living accommodation. There were 4196 uncompleted returned forms, representing 8.5% of the overall population who were contacted.

Of the returned index sibling questionnaires, name and contact information was provided for 11 656 non-index siblings. By March 1999, 3682 non-index siblings had returned questionnaires. Table 1 shows the total number of families and sibling pairs in the GENESiS study. Families with more than two siblings generate larger numbers of possible sibling pairs. Thus a family with three siblings generates 3 sibling pairs, whilst a 4-sib family generates 6 sibling pairs. This meant that 2658 families generated a total number of 3944 sib pairs.

The sociodemographic characteristics of the sample are shown in Table 2. There is a fairly uniform age distribution and a slight predominance of females (58%). The sample is 98% Caucasian, which is advantageous for a genetic study to map QTLs. There is a good spread of socio-economic status in the sample.

Summary statistics

The means of the four measures shown in Table 3 indicate a generally higher level of anxiety and depression in females than in males, which is consistent with the higher prevalence of depression

Table 1 Distribution of sibship size in the GENESiS study

Sibship size	Number of sibships	Number of individuals
2	2157	4314
3	417	1251
4	76	304
5	8	40
Total	2658	5909

Table 2 Socio-demographic characteristics of GENESIS sample: whole sample, n=17, 301 including singleton families; Sibships, n=3109 (ie excluding singleton families)

Socio-demographic characteristics	Whole sample, %	Sibships %		Whole sample, %	Sibships %
Age			Employment		
20–29 years old	16	12	Manager	15	16
30–39 years old	29	31	Professional	17	23
40–49 years old	31	35	Associate professional/technical	7	6
50+ years old	24	22	Clerical/secretarial	13	13
Gender			Craft/manual	8	5
% male	42	36	Service	7	5
Ethnicity			Sales	6	5
% white	98	99	Plant/machine operative	2	2
Accommodation			Looking after home	12	10
Own home	76	82	Unemployed	3	2
Rent	10	8	FT student	2	2
LHA/council	5	4	Self-employed	6	7
Living with parents	8	5	Never-worked	0.3	0.1
Other	1	1	Other	2	4
Religion			Highest educational level		
% not religious	75	81	No qualifications	16	10
			CSE	9	8
			O-level/GCSE	31	30
			A/AS/S level	14	15
			HNC	5	4
			HND	4	4
			Degree	16	22
			Postgraduate	5	7

Table 3 Summary statistics of anxiety/depression measures; means and standard deviations (*italics*)

Age band	GHQ-12		EPQ-N		HPA		AA	
	Male	Female	Male	Female	Male	Female	Male	Female
20s	11.34	12.94	5.08	6.55	30.01	27.70	14.95	15.05
	5.60	5.77	3.32	3.11	8.28	8.52	5.63	5.61
30s	11.63	12.71	4.50	6.00	29.13	27.29	13.57	13.83
	5.58	5.76	3.40	3.19	7.97	8.30	5.04	5.02
40s	11.57	12.61	4.26	5.65	28.69	27.12	13.17	14.00
	5.38	5.76	3.29	3.33	7.96	8.27	4.82	5.31
50s	11.44	12.22	3.98	5.26	28.57	27.59	12.87	14.06
	5.49	5.60	3.36	3.30	8.15	8.18	4.59	4.87

GHQ-12: General Health Questionnaire, 12-item version; EPQ-N: Eysenck Personality Questionnaire, Neuroticism; HPA: MASQ High Positive Affect (depression, reverse scoring); AA: MASQ Anxious Arousal.

in women reported in previous epidemiological surveys.²⁷ There also appears to be a consistent decline of neuroticism with increasing age in both males and females.

The correlations between the four measures, both within individuals and between siblings, are shown in Table 4. The four measures are inter-related within individuals, as indicated by the high within-sib/cross-traits 'phenotypic' correlations. They are heritable to varying degrees, as indicated by the modest between-sibs/same-trait correlations. They also appear to share a common genetic basis, as indicated by between-sibs/cross-traits correlations that are

almost as large as the between-sibs/same-trait correlations.

Model-fitting

The results of model-fitting, as shown in Table 5, favour a model with a common familial factor that loads substantially on all four measures, explaining 23%, 18%, 15% and 20% of the variance of EPQ-N, GHQ-12, MASQ-AA and MASQ-HPA, respectively (Common F, Cholesky E in Table 5). Measure-specific genetic components accounted for a further 14%, 2%, 5%, 11% of the variance of these four measures,

Table 4 Correlation matrices for the four main anxiety/depression measures

	N	GHQ	HPA	AA
(a) Phenotypic correlations (n=17031, including singleton families)				
N	1.00			
GHQ	0.5491	1.00		
HPA	-0.4617	-0.5518	1.00	
AA	0.3952	0.4267	-0.3827	1.00
(b) Cross-sibling correlations (n=3109), same-trait (bold) and cross-trait				
N	0.1682	0.0877	-0.0962	0.0654
GHQ	0.1056	0.0936	-0.0884	0.0506
HPA	-0.0760	-0.0683	0.1862	-0.0955
AA	0.0783	0.0843	-0.1589	0.1363

Note: asymmetry due to single-entry for cross-sibling correlations.

Table 5 Fit indices from fitting multivariate genetic models to depression/anxiety variables

Model	-2lnL	df	Δ -2lnL	Δ df	P
Saturated model	58985.024	22482	0	0	-
Cholesky F, Cholesky E	59209.194	22688	244.170	206	0.183
Common F, Cholesky E	59210.336	22690	225.312	208	0.195
Cholesky F, Common E	59280.406	22690	295.382	208	0.0001
Common F, Common E	59340.175	22692	355.151	210	0.0000

F: Familial (genetic & environmental); E: non-shared environment.

leading to heritability estimates of 37%, 20%, 20%, 31%, respectively. The path diagram of this model is shown in Figure 1.

Creation of composite index

Using the estimated path coefficients from the common genetic factor to the four measures in the best model, and the estimated correlation matrix of the four measures, we used the method of Thomson²⁸ to compute factor scores of the common genetic factor. Let x be a column vector of the observed values of the 4 standardised measures in an individual, then the factor score y of the individual is given by the expected value of the general factor conditional on x , which under the assumption of multivariate normality is given by:

$$y = \lambda \Sigma^{-1} x$$

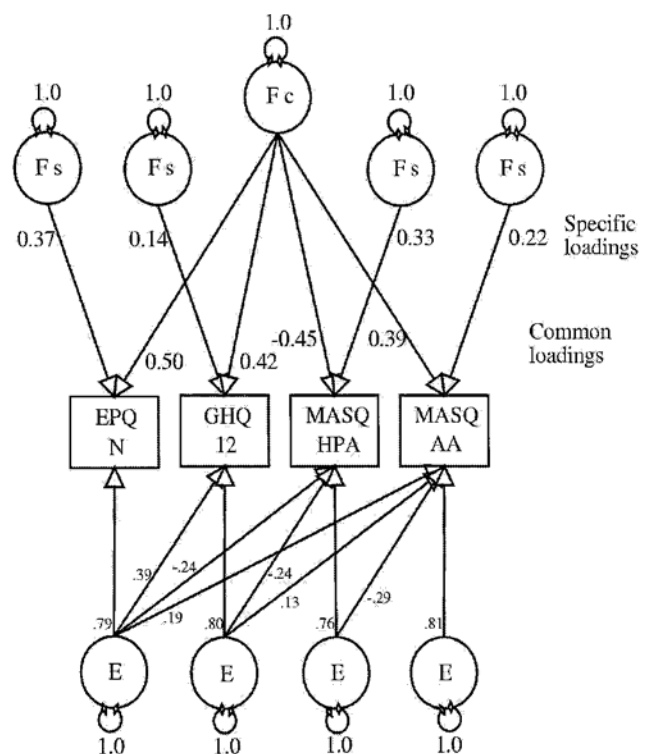
where λ is a column vector of the estimated path coefficients (which represent the correlations between the common genetic factor and the four measures), Σ is the correlation matrix of the four measures. From the estimated values of λ and Σ , the regression coefficients of the four measures EPQ-N, GHQ-12, MASQ-HPA and MASQ-AA, given by the elements in $\lambda \Sigma^{-1}$, are 0.259, 0.103, -0.204 and 0.163, respectively. The factor score y calculated using these regression coefficients, will be used as a composite index of the underlying common genetic factor in further analyses of this sample. The uni-

variate frequency distribution is shown in Figure 2; the sibling correlation of this complete index was 0.22.

We also constructed four other composite indices using the same method, each leaving out one of the four measures. These incomplete indices serve to provide a 'surrogate' for the complete index when one of the four measures is actually missing. The correlations between the complete index and the four incomplete indices are high (see Table 6).

Discussion

We studied the familial architecture of four measures of anxiety and depression in a community sample of sibships, in preparation for future molecular genetic analyses to identify quantitative trait loci. The heritability estimate of 37% for EPQ-N is comparable to those obtained from other family and adoption studies. For example, in the largest family study of personality, correlations for first-degree relatives for personality, including neuroticism are about 0.15, suggesting an upper-limit heritability estimate of



Key:
F c = Familial component (additive genetic and shared environmental) common to all measures.
F s = Familial components specific to individual measures.
E = Nonshared environmental components.

Figure 1 Common familial factor model

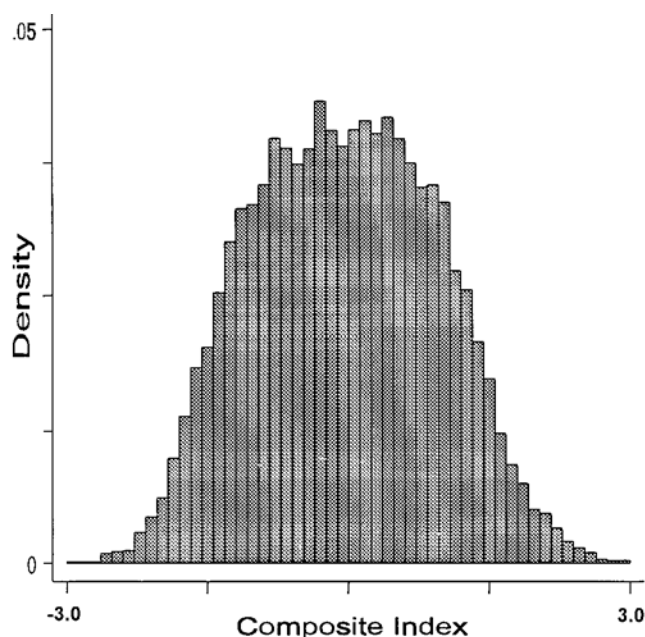


Figure 2 Phenotypic distribution of the composite index derived from GHQ-12, EPQ-N, MASQ-HPA and MASQ-AA in the GENESiS sample

Table 6 Correlations between complete and incomplete composite indices (n=19200 individuals)

	Complete	EPQ-N missing	GHQ missing	HPA missing	AA missing
Complete	1.0000				
EPQ-N missing	0.9305	1.0000			
GHQ missing	0.9906	0.9001	1.0000		
HPA missing	0.9568	0.8544	0.9309	1.0000	
AA missing	0.9679	0.8733	0.9504	0.9085	1.000

about 30%.²⁹ Heritability estimates from twin studies are higher,³⁰ perhaps because monozygotic twin correlations include a greater amount of non-additive genetic variance than first-degree relatives such as siblings.³¹ This suggests that most of the genetic variance of neuroticism is additive, which is an important issue in relation to QTL analyses because non-additive genetic variance complicates attempts to find QTLs.

As hypothesised, quantitative genetic model fitting provided support for a single genetic vulnerability factor that is shared by EPQ-N, GHQ12, MASQ-HPA and MASQ-AA. We were able to derive from the parameter estimates of the best model a single composite index of the common familial vulnerability factor. This measure had a sib correlation of 0.22, which is greater than the sib correlation of any of four component scales. The greatest contribution of EPQ-N to the composite index is consistent with the substantial evidence in the literature that EPQ-N is a relatively stable trait measure of emotional instabil-

ity that is closely related to vulnerability to depression.

A limitation of the GENESiS project is the inability of the sib-pair design to separate out shared environmental influences from genetic effects. All heritability estimates derived in this study are therefore subject to the assumption that shared family environment is absent. However, while this assumption cannot be tested in GENESiS, it has been demonstrated to be approximately valid in large-scale twin studies.^{14,32}

The ultimate aim of the GENESiS project is to identify quantitative trait loci (QTLs) for the shared genetic vulnerability to anxiety and depression rather than trying to identify QTLs separately for anxiety and depression. We also aim to characterise the interactions between these QTLs and psychosocial adversity in the aetiology of anxiety and depressive disorders. The demonstration of a single dimension of vulnerability to anxiety and depression in this sample of siblings offers support for adopting a QTL approach to genetic mapping. The composite index that we have constructed to measure this vulnerability dimension will be used in future molecular genetic studies on this sample.

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