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A population-based study of personality in 34 000 sib-pairs

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Several theoretical studies have suggested that large samples of randomly ascertained siblings can be efficiently used to ascertain phenotypically extreme individuals and increase power to detect genetic linkage. Phenotypes that can be reliably measured by questionnaire are of obvious utility for such selection strategies, as large numbers of individuals can be contacted without laborious individual interview. As the first step in developing a large randomly-ascertained family cohort in southwest England, a sample of 88 000 individuals, including more than 34 000 sibling pairs in 20 000 sibships, was administered the Eysenck Personality Questionnaire (EPQ) by commercial mailing. The sample age ranges were 20–67 years and comprised 59% males and 41% females. Descriptive properties of the EPQ scales are similar to those reported from other large family cohorts. Test–retest correlations on 1681 probands in the sample are substantial for the N-scale (r = 0.93), but somewhat more modest for the other scales (range r = 0.70–0.88). Phenotypic and sibling correlations correspond quite closely to those of twin studies. Twin Research (2000) 3, 310–315.

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Introduction

One of the many reasons for the lack of success in mapping susceptibility loci for psychiatric disorders is that the intensive interviewing necessary for reliable diagnosis has prohibited the collection of the large sample sizes needed to detect small genetic effects: it has been estimated that tens of thousands of cases may be required to obtain adequate power.[1] In some cases it may be possible to collect sufficiently large samples by using phenotypes correlated with psychiatric illness, thus avoiding the need for time-consuming and expensive interviews. One example is the personality trait neuroticism, known to be a mediator of major depression and generalised anxiety disorder.

Most trait psychologists agree that neuroticism (or emotional instability) is a major factor in personality,[2–6] defined, for instance, by different personality schedules such as the Eysenck Personality Questionnaire (EPQ),[7,8] Revised NEO Personality Inventory and Big Five Inventory.[9] Genetic research has been instrumental in providing biological validation of neuroticism (N).

The cumulative evidence from the wide range of twin, adoption and nuclear family studies indicates a moderate role of genetic factors and fewer, if any, effects of the shared family environment on major personality dimensions.[10] For neuroticism, additive and non-additive genetic influences account for about 27–31% and 14–17% of the variability in the EPQ neuroticism scale, respectively.[11] These general heritability trends, coupled with observations of differences in genetic influences on males and females and the paucity of evidence for shared environmental effects, have recently been confirmed in large twin studies from Australia, the United States and Finland, ranging in size from 7000 to 25 000 individuals.[10,12,13]

In prospective studies, neuroticism is the only personality trait consistently associated with depression[14–17] and much of the phenotypic correlation represents genetic correlation with N Eaves et al's[18] present evidence that individuals with high N have a high chance of suffering from symptoms of anxiety and depression, whilst analysis of twin data shows that around 55% of the genetic liability of major depression is shared with neuroticism.[19,20] Jardine et al's[21] multivariate analysis of 3810 twin pairs led to

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the conclusion that the genetic basis of neuroticism accounted for 92% of the genetic variation of anxiety, and 83% of the genetic variation of depression.

It remains to be seen whether it is possible to map specific loci that contribute to variability in N, and whether, as expected, these loci also contribute to depression and anxiety disorders. As it is well known that samples of 10 000s or more of randomly selected sibships are required to detect linkage for loci of even moderate effect size, very large cohorts of at least the size of the US, Finnish and Australian samples noted above will be necessary to identify susceptibility loci. The large size and scope of these studies also renders them suitable for various phenotypic selection schemes, thereby reducing the genotyping burden while maintaining statistical power.[22–26]

We have conducted a population-based study of personality in southwest England, in which over 88 000 individuals (including more than 34 000 sibling pairs) completed the EPQ. The primary aim of this study was to ascertain a large random sample of sibling pairs from which we could select specific phenotypic extremes to genotype in a linkage study of neuroticism. Here we describe the design of this study, test–retest correlations and sibling correlations as indicators of familial resemblance for the primary EPQ scales.

Methods and results

Sample collection

In the United Kingdom, practically all the names and addresses of the British population are contained in the lists of general practitioners.[27] After acquiring appropriate ethical permissions, we used this resource to contact a large initial cohort (n = 100 000) through the patient registers of general practices in four counties in the Southwest of England: Oxfordshire, Gloucestershire, Somerset and Berkshire. Given some preliminary expectations of 'proband' response rates (55%) and sibling referral (70%) and follow-up (80%) based on a small pilot study in the same catchment area, we expected this initial cohort to yield EPQ data from approximately 30 000 sibling pairs.

Because of the large size of the data set and in order to collect the data as quickly as possible, we used a commercial mailing organisation (National Computer Services, Rotherham, UK). Data from GP registers were acquired electronically and used to establish a database from which EPQ forms with the appropriate addresses were generated. Subsequently EPQ data from returned forms, and the names and addresses of siblings were entered into the database using the company's software.

The initial cohort of 100 000 patients, aged between 30 and 50 years, were sent the EPQ and a request for the names and addresses of any siblings, a covering letter from their general practitioner and a stamped addressed envelope. Of these 100 000, only 35% responded to the first mailing. This lower than expected response rate was in part due to unexpected inaccuracies in the lists of names and addresses provided by the general practitioners. Therefore, we doubled the number of request letters and conducted a secondary mailing. From this mailing and a subsequent follow-up mailing to siblings identified by the initial respondents, we received responses from a total of 88 141 individuals, including 20 427 unique sibships. Most of the sibships consisted only of the proband and one additional sibling (15 259/20 427 = 75%) but larger sibships of sizes 3, 4, 5 and 6 were also identified (n = 4146, 838, 151 and 23, respectively). The total sample thus consists of 34 580 sib pairs in 20 427 sibships. Of the total respondents, 46% (40 915/88 141) provided no information about other relatives. Of the total sample, 52 249 (59.3%) were male and 35 892 (40.7%) were female.

The mean age of the total sample is 40.31 years, with a range of 20–67 years. Females were slightly older than males in the both proband ($t = 5.02$, $P < 0.001$) and sibling ($t = 5.06$, $P < 0.001$) categories. The age distribution of the sample is shown in Table 1.

Phenotypic measures

The full 90-item revised EPQ[7] was sent to all study participants. The EPQ scales of neuroticism (N), extraversion (E), psychoticism (P) and lie (L) were constructed from the individual items according to the questionnaire guidelines. Following the suggestions of Eaves et al,[18] angular transformations were applied to the neuroticism (N), extraversion (E), and

Table 1 Ages and sample sizes for final respondents[a]

Respondent	n	Mean	Std Dev	Min	Max
All:	88 141	40.31	6.83	20	67
Male	52 249	40.13	6.85	20	67
Female	35 892	40.58	6.78	20	67
Probands:	20 427	40.40	6.07	29	51
Male	12 836	40.24	6.10	29	51
Female	7 579	40.68	6.02	29	51
Siblings:	26 799	41.00	8.25	20	67
Male	16 186	40.79	8.26	20	67
Female	10 613	41.31	8.21	20	67

[a]Probands' respondents in the initial cohort whose sibling(s) also responded to the questionnaire.

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lie (L) scales in attempt to minimise correlations between means and variances within sibling pairs. This transformation is formulated as $_{\text{arcsin}}\sqrt{x/m}$, where x is the number of items scored positively by a subject on a particular scale and m is the maximum possible score on that scale (m = 23, 21 and 21 for N, E and L, respectively). Psychoticism (P) scores were transformed by taking the square root of the sum of the items correctly scored in the direction of P.

Descriptive statistics for the transformed EPQ scales in this sample are presented in Table 2. The transformed data for each scale were evaluated by factorial ANOVA to assess mean differences as a function of gender and age. All scales showed mean differences for gender (Table 2), as well as significant main effects for age as described above. Age by gender interactions were also significant at the 0.01 level or greater for several scales. These results are unsurprising given that the large size of this study renders even small differences statistically significant. For these descriptive statistics, we have excluded additional siblings beyond the core sib-pair in order to simplify presentation. The results for the other siblings are fully consistent with those presented in Table 2 (data not shown). All data presented henceforth refer to transformed scales after age, gender and age by gender correction (via multiple regression), unless noted otherwise.

Measurement reliability

As with virtually any psychometric scale, a proportion of the phenotypic variance of the EPQ is expected to be due to short-term mental state effects. To quantify this source of variation, we re-screened a subset of the sample (n = 1618) 18 months after the initial questionnaire was returned. For neuroticism, the test–retest correlation was reasonably high (r = 0.932), suggesting largely consistent measurement in this sample. The test–retest correlations among the P, E, and L scales were somewhat more modest, at 0.694, 0.884 and 0.796, respectively.

Table 2 Descriptive statistics for 20 415 unique sibling pairs

Respondent group	measure	Total mean (SD)	Male mean (SD)	Female mean (SD)	Gender t	P
Probands	P	1.41 (0.78)	1.29 (0.77)	1.63 (0.77)	–30.550	<0.001
	E	0.87 (0.30)	0.88 (0.30)	0.85 (0.30)	6.200	<0.001
	N	0.79 (0.29)	0.83 (0.28)	0.71 (0.30)	29.910	<0.001
	L	0.70 (0.20)	0.73 (0.20)	0.65 (0.20)	25.871	<0.001
Siblings	P	1.45 (0.79)	1.33 (0.77)	1.66 (0.77)	–29.568	<0.001
	E	0.87 (0.30)	0.87 (0.30)	0.87 (0.30)	1.303	0.193
	N	0.77 (0.30)	0.83 (0.29)	0.69 (0.30)	31.688	<0.001
	L	0.70 (0.21)	0.73 (0.21)	0.66 (0.21)	24.252	<0.001

Of the original 20 427 proband–sibling pairs, 12 were found to have incomplete data and so were excluded from all analyses. Consequently, these values were calculated from 40 830 individuals (12 836 proband males, 7 579 proband females, 12 581 sibling males, 7 834 sibling females). All scales were transformed using the procedure suggested by Eaves et al[18] as described in the text.

Sibling correlations

The phenotypic and cross-sibling correlations among the P, E, N and L scales are shown in Table 3. The top panel reflects correlations for the entire sample after angular and square root transformations as described above, and after removing the effects of gender and age by multiple regression. The EPQ scale correlations for same sex and opposite sex siblings are also shown in the lower B and C panels of Table 3, respectively. Of primary interest in these correlations are the cross-sibling relationships for the different EPQ scales (shown in bold). Overall, the sibling correlations for P, E, N and L are 0.11, 0.17, 0.17, and 0.14, respectively. These correlations reflect the averaging effects of the slightly higher female correlations and lower male and opposite sex correlations. As described above in our mean comparisons, we have once again excluded additional siblings beyond the core sibship in these correlations to simplify presentation.

Collection of buccal swabs and DNA extraction

It is known that appropriate sub-sample selection strategies can extract most of the genetic information from much larger samples and together with maximum likelihood methods for linkage analysis enable the localisation of QTLs with small effect (with a heritability of 10%). Using our large sample, we have begun collection of a sub-sample of sib pairs selected for their apparent informativeness for linkage studies on the basis of their joint phenotypic extremity. Pairs have been selected using a flexible algorithm that selects both concordant extreme pairs and extremely discordant pairs. The use of both types of extreme pairs is believed to improve efficiency[28,29] and to be more robust than sampling only concordant or only discordant pairs against potential decrements in power that may occur when extreme sampling is used and one is searching for common polymorphisms of moderate effect.[30]

We received swabs from 2491 individuals, comprising 807 families. We wrote to the parents of all families and received swabs from both parents for 302 families and from one parent for 335 families. There was no significant difference in the N scores

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Table 3 Phenotypic correlations between and within siblings.[a] The top panel (A) represents the total correlation structure, collapsed across genders. The same-sex and opposite-sex correlations are shown in panels B and C, respectively.

A		Proband				Sibling			
		P	E	N	L	P	E	N	L
Proband	P								
	E	0.096							
	N	0.089	–0.246						
	L	–0.226	–0.127	–0.101					
Sibling	P	0.118	0.033	0.022	–0.039				
	E	0.029	0.164	–0.047	–0.011	0.099			
	N	0.032	–0.039	0.171	–0.014	0.096	–0.245		
	L	–0.045	–0.023	0.004	0.145	–0.225	–0.124	–0.115	

B		Proband				Sibling			
Female pairs		P	E	N	L	P	E	N	L
Proband	P		0.089	0.088	–0.225	0.130	0.025	0.038	–0.039
	E	0.139		–0.266	–0.121	0.021	0.178	–0.055	–0.033
	N	0.086	–0.200		–0.090	0.037	–0.062	0.181	0.015
	L	–0.250	–0.142	–0.093		–0.036	–0.025	–0.003	0.151
Sibling	P	0.133	0.061	0.010	–0.042		0.103	0.092	–0.206
	E	0.004	0.171	–0.016	–0.020	0.095		–0.268	–0.107
	N	0.002	–0.019	0.186	–0.027	0.096	–0.185		–0.125
	L	–0.060	–0.021	–0.011	0.146	–0.228	–0.138	–0.123	

C		Proband				Sibling			
		P	E	N	L	P	E	N	L
Proband	P								
	E	0.088							
	N	0.090	–0.246						
	L	–0.221	–0.127	–0.112					
Sibling	P	0.104	0.035	0.013	–0.041				
	E	0.041	0.150	–0.046	–0.010	0.096			
	N	0.037	–0.031	0.157	–0.019	0.100	–0.246		
	L	–0.044	–0.015	0.001	0.141	–0.240	–0.134	–0.104	

[a]All scales were transformed and age and gender corrected as described in the text.

between families that returned a swab and those that did not.

DNA was extracted from the buccal swabs by vortexing the end of the swab in 500 μl 50 mM NaOH in a 1.5 ml Eppendorf tube. After 10 mins at 95°C, 50 μl of 1 M Tris (pH 8.0) were added and the mixture vortexted for 30 s. 200 μl of a commercially available matrix (Biorad Hercules, CA, USA) was added, the mixture incubated at 56°C for 30 mins, followed by heating at 100°C for 8 mins. After removing the brush, the tube was spun at 12 000 rpm for 3 min and the supernatant transferred to a new tube for PCR.

In order to provide enough DNA for a complete genome scan (about 300 microsatellite markers) we used a modified primer extension preamplification protocol (PEP) on DNA extracted from the buccal swab.[31] 5 μl of template DNA was added to a mix of 2.5 μl dNTP (8 mM), 4 μl MgCl2 (25 mM), 10 μl PCR buffer (Roche Diagnostics, Lewes, UK), 20 μl $(N)_{15}$ oligonucleotides (200 μM) (Sigma-Aldrich, Poole, UK), 0.5 μl AmpliTaq Gold and water to make a final volume of 100 μl. PEP was performed on an MJ thermocycler using mineral oil to seal the reaction, with the following cycling parameters: an initial denaturation at 95°C for 18 min, followed by 49 cycles of 95°C for 1 min, 37°C for 2 min ramping to 55°C at 0.1 °C/s with a final extension at 72°C for 5 min. We used 1 μl of the PEP reaction mix for subsequent PCRs and found that 98% of PEP DNAs gave readable genotypes. A second PEP reaction was performed on those DNAs that failed to amplify the first time. Each swab yielded enough DNA for 100 PEP reactions, so we have more than sufficient quantities of DNA for a genome scan.

Discussion

Over an 18-month period we collected EPQ data from 88 000 individuals, including 34 000 sib pairs in 20 000 sibships. We have demonstrated that using commercially available mailing resources it is possible to collect sample sizes large enough to detect small genetic effects within a relatively short space of time. The dataset provides a resource from which

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to identify extreme discordant and concordant sib pairs[26,29] suitable for genetic mapping studies.

Our data can also be used to estimate the genetic contribution to personality traits. Although sibling correlations reflect both genetic and environmental resemblance, it is possible to disentangle the two influences since shared environmental effects are unlikely to have a substantial impact on EPQ-score variability.[18] Consequently the (same sex) sibling correlations in Table 3 may reflect only the broad-sense genetic variance, comprising both additive and dominant genetic effects.

The sibling correlations presented in Table 3 are congruent with those described recently by Lake et al[12] in large Australian and US samples of twins and relatives. In the Lake et al data, which involved only the neuroticism scale, non-twin sibling correlations ranged from 0.11 (male) to 0.17 (female) in the US samples and from 0.11 (opposite sex) to 0.14 (female) in the Australian samples. These are similar to those shown in Table 3, although our male correlations are slightly higher than those previously observed. Moreover, model-fitting results from the full twin/family samples of Lake et al revealed (standardised) additive genetic variances of 0.28 and 0.25 and non-additive genetic variances of 0.13 and 0.10 for females and males, respectively. These parameter estimates imply a female sib-correlation of 0.17 and a male correlation of 0.15. The respective correlations in the present sample are both 0.18, again demonstrating consistency across these studies.

Investigation of the phenotypic correlations between N, depression and anxiety, together with multivariate genetic analyses of twin studies indicate that the genes that predispose to neuroticism appear largely to overlap with those that predispose to two common affective disorders, depression and generalised anxiety disorder. The genetic influences on neuroticism in our very large sample of siblings appear to be the same as in the twin studies. We anticipate that our sample will be suitable for mapping susceptibility loci for N, which we expect will also influence depression and some forms of anxiety.

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