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Dimensions of temperament as vulnerability factors in depression

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In order to evaluate the hypothesis that one set of genetic risk factors may be common to disorders and dimensions of temperament, whereas environmental risk factors are disorder specific, we have conducted a genetic analysis of dimensions of temperament and symptoms of depression in about 201 pairs of monozygotic and dizygotic twins. Dimensions of temperament associated with novelty seeking, harm avoidance, reward dependence, and persistence were measured by using the Temperament and Character Instruments developed by Cloninger, and depressive symptoms were measured using the Hospital Anxiety and Depression Scale. Differences among individuals on these measures can be explained by differences in their genes and in their environmental experiences. There are no differences between the sexes in gene action affecting temperament. Each dimension of temperament is genetically dependent, and genetic variations in symptoms of depression are largely dependent on the same factors that affect the temperament. Temperament is closely associated with vulnerability to depressive symptoms.
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Although the heritability of liability to major depression in most twin studies ranges from 31% to 42%,[1] it remains unclear whether depression itself is inherited or some personality traits vulnerable to mood disorders are inherited.[2] Many authors have suggested that a certain type of personality or temperament is at high risk for developing major depression.[3–10] Kendler *et al*,[6] for example, reported that the correlation between neuroticism and the liability to major depression is substantial and that most observed correlations were due to genetic factors that influence both traits. Data on the genetics of the relationship between dimensions of temperament and minor depression are much less clear, although most studies reported that less severe conditions such as neurotic depression or dysthymic disorder showed no heritability.[11]

Considering the possibility that common behavioral disorders including depression represent the genetic extremes of a continuum,[12] we could hypothesize that what is inherited is a temperament that predisposes vulnerability to depression, the expression of which will ultimately be determined by environmental factors. In order to evaluate this hypothesis, we have conducted a genetic analysis of dimensions of temperament and mild depression in monozygotic (MZ) and dizygotic (DZ) twins.

Table 1 shows the means and SDs of the five phenotypic scores of our 201 twin pairs. The mean scores of temperament dimensions of Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RA), and Persistence (P) measured by Cloninger *et al*'s Temperament and Character Inventory (TCI),[13,14] and depressive symptoms measured by Hospital Anxiety Depression Scale (HADS-D)[15,16] were 20.93, 18.73, 15.41, 4.58, and 4.18 respectively. According to Kijima *et al*'s report,[17] the Japanese sample mean scores of NS, HA, RA, P were 19.4 (SD = 5.4), 16.5 (SD = 6.4), 8.9 (SD = 4.1), and 3.7 (SD = 2.0) respectively, whereas those of the

Table 1 Descriptive statistics of TCI (temperament) and HADS (depression)

	Mean	*SD*	*n*
NS	20.93	5.38	402
HA	18.73	6.71	402
RD	15.41	3.69	402
P	4.58	1.96	402
HADS-D	4.18	2.60	402

NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; P = Persistence; HADS-D = depression.

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Table 2 Phenotypic twin correlation of TCI (temperament) and HADS (depression scales)

	MZf	*DZf*	*MZm*	*DZm*	*DZo*
NS	0.095	0.094	0.421	0.102	0.322
HA	0.241	0.243	0.502	−0.212	0.244
RD	0.416	0.197	0.330	0.214	0.241
P	0.335	−0.162	0.357	0.238	−0.454
HADS-D	0.364	0.266	0.509	0.286	0.094

USA samples reported by Cloninger *et al*[18] were 19.2 (SD = 6.0), 12.6 (SD = 6.8), 15.5 (SD = 4.4), and 5.6 (SD = 1.9) respectively. The scores of all four dimensions of our participants are significantly higher than those of Japanese samples and the scores of NS and HA of our participants were significantly higher than those of the USA samples and the score of P is significantly lower than that of the USA samples.

Although Japanese population means of the HADS score have not been reported, an optimal cut-off point in screening for adjustment disorder and major depressive disorder is 10/11, and 19/20 is an optimal cut-off point for major depressive disorder alone according to Kugaya *et al*'s report.[19] Among the 402 study participants in our sample, 197 (49.0%) scored below 10, 175 (43.5%) between 11 and 19, and 30 (7.5%) above 20. Although we cannot directly compare the HADS data of the Japanese version and that of English version, the mean HADS depression scores of our participants were significantly higher than those of an American comparison group (mean = 1.68, SD = 2.36) reported by Clarke *et al*.[20]

To check for a genetic contribution, twin similarities were compared for zygosity (Table 2). For the TCI scales and HADS-D, MZ correlations exceeded DZ ones except for NS and HA in females, indicating a genetic contribution to personality development and the formation of depressive symptoms. Univariate genetic analysis was conducted to obtain the appropriate estimates of genetic and environmental parameters (additive and nonadditive genetic/shared and nonshared environmental factors) via structural equation modeling with the maximum likelihood technique using EQS.

For all dimensions except RD, no-sex or general AE model was the best fit (Table 3). For RD, the no-sex AE and CE models show almost the same fit. The relative contributions of genetic and environmental parameters under the best fitting models for the four temperament dimensions as well as depression were calculated.

Table 3 Relative contributions and fitness of additive G(a)/shared E(c) nonshared E(e) factors (univariate genetic analysis)

		NS	*HA*	*RD*	*PS*	*DEP*
No sex-limitation						
ACE	χ^2	15.503	8.749	3.803	25.092	9.023
	P	0.215	0.724	0.987	0.014	0.701
df = 12	AIC	−8.497	−15.251	−20.197	1.092	−14.98
ADE	χ^2	13.249	68.385	18.732	31.735	9.051
	P	0.351	<.001	0.095	0.002	0.699
df = 12	AIC	−10.751	44.385	−5.268	7.735	−14.95
AE	χ^2	6.490	8.785	4.069	7.287	9.051
	P	0.926	0.789	0.990	0.887	0.769
df = 13	AIC	−19.510 ‡	−17.215 ‡	−21.931 †	−18.713 ‡	−16.95 ‡
CE	χ^2	8.115	9.047	3.804	9.240	11.494
	P	0.836	0.769	0.993	0.755	0.57
df = 13	AIC	−17.885	−16.953 †	−22.196 ‡	−16.760	−14.51
Sex limitation						
		NS	HA	RD	PS	DEP
ACE	χ^2	42.133	8.309	3.439	4.170	7.060
	P	<.001	0.503	0.944	0.900	0.631
df = 9	AIC	24.133	−9.691	−14.561	−13.830	−10.940
ADE	χ^2	13.908	10.974	12.207	3.275	7.360
	P	0.126	0.278	0.202	0.952	0.600
df = 9	AIC	−4.092	−7.026	−5.793	−14.725	−10.640
AE	χ^2	6.388	8.336	3.859	5.958	7.406
	P	0.846	0.683	0.974	0.876	0.765
df = 11	AIC	−15.612	−13.664	−18.141	−16.042	−14.590
CE	χ^2	8.093	8.688	3.641	8.806	9.768
	P	0.705	0.651	0.979	0.640	0.551
df = 11	AIC	−13.907	−13.312	−18.359	−13.194	−12.230

† The best.
‡ The second best.

Table 4 Relative contributions of genetic and environmental parameters

		NS	*HA*	*RD*	*P*	*HADS-D*
AE	a	0.18	0.35	0.40	0.29	0.40
	e	0.82	0.65	0.60	0.72	0.59

Under the no sex-limitation AE models, the genetic contributions of NS, HA, RD, P, and HADS-D were 18, 35, 40, 29, and 40%, respectively (Table 4).

In order to examine relationship between temperament dimensions and depression, the correlation matrix among these five scores of two sets of twins is shown in Table 5. As this table shows, cross correlation between HA of twin 1 and HADS-D of twin 2 (or HA of twin 2 and HADS-D of twin 1) in MZ pairs is higher than in DZ pairs (0.323, 0.196 *vs* 0.214, 0.082). Similarly cross correlations between RD and HADS-D for MZ pairs are also higher than those for DZ pairs (−0.336,−0.191 *vs* −0.131,−0.123). These results suggest that depression may be genetically mediated by HA and RD. To verify this hypothesis and depict the genetic and environmental relationship between temperament dimension and depression, multivariate genetic analysis was conducted.

Because no dimensions showed any sex-limitation AE models in the univariate genetic analysis, only the no-sex AE model was considered in this multivariate genetic analysis. Table 6 shows the additive genetic and nonshared environmental correlations among the TCI dimensions of temperament scales and the HADS-D scale calculated from solutions under the Cholesky decomposition model. Substantial genetic correlations were found in NS and P (−0.48), HA and HADS-D (0.71), and in RD and HADS-D (−0.65). There were also substantial environmental correlations in P and HA (−0.61), and HA and NS (−0.51). As this table indicates, four dimensions of temperament and depressive symptoms were environmentally independent but genetically overlapped.

Table 6 Genetic (lower) and environmental (upper) correlations

	NS	*HA*	*RD*	*P*	*HADS-D*
NS		−0.51	0.07	−0.11	−0.11
HA	−0.15		−0.06	−0.61	0.19
RD	0.27	−0.13		0.06	0.02
P	−0.48	−0.23	0.20		−0.16
HADS-D	−0.29	0.71	−0.65	0.04	

Table 7 Comparison of different genetic structure models for four temperaments and depression

Model	χ^2	*df*	*P*	*AIC*
Base (Cholesky)	267.397	245	0.156	−222.603
4 G	267.420	246	0.166	−224.6
3 G	269.984	248	0.161	−226.0
3 Specific G	271.589	251	0.178	−230.0

Because of the genetic overlap of these five phenotypic factors, several plausible hypothetical models were compared to identify more simple genetic structures. Table 7 provides fit statistics of various plausible models. The first model is the Cholesky decomposition model which assumes no specific structure as a base model. Considering the basic characteristics of genetic and environmental overlap between temperament dimensions and depression, two other models were compared with the Cholesky model. The four-factor model assumed that four genetic factors corresponding to NS, HA, RD, and P affected depression in a Cholesky fashion. Fitness was slightly improved, and AIC was −224.60. The three-factor model assumed that there were three latent genetic factors. According to AIC

Table 5 The correlation matrix among the five phenotypic scores of the two sets of twins

		Twin 1					*Twin 2*				
		NS	*HA*	*RD*	*P*	*HADS-D*	*NS*	*HA*	*RD*	*P*	*HADS-D*
Twin 1	NS		−0.259	0.107	−0.288	−0.127	0.173	0.024	−0.038	0.130	−0.007
	HA	−0.381		0.017	−0.078	0.336	−0.039	0.170	0.021	−0.038	0.214
	RD	0.159	−0.070		0.185	−0.303	0.082	0.047	0.151	−0.039	−0.132
	P	−0.283	−0.033	0.094		−0.121	−0.024	0.020	0.080	−0.164	−0.131
	HADSD	−0.007	0.349	−0.232	−0.053		−0.077	0.082	−0.123	0.180	0.239
Twin 2	NS	0.180	−0.145	0.054	−0.171	−0.139		−0.381	0.240	−0.185	−0.262
	HA	0.023	0.320	−0.136	−0.116	0.323	−0.539		−0.087	−0.168	0.343
	RD	0.057	−0.016	0.393	−0.027	−0.336	0.055	−0.166		0.017	−0.255
	P	−0.080	−0.049	0.168	0.326	−0.052	−0.080	−0.323	0.142		−0.048
	HADSD	−0.007	0.196	−0.191	0.004	0.400	−0.218	0.434	−0.249	−0.123	

Below diagonal, MZ correlation. Above diagonal, DZ correlation.

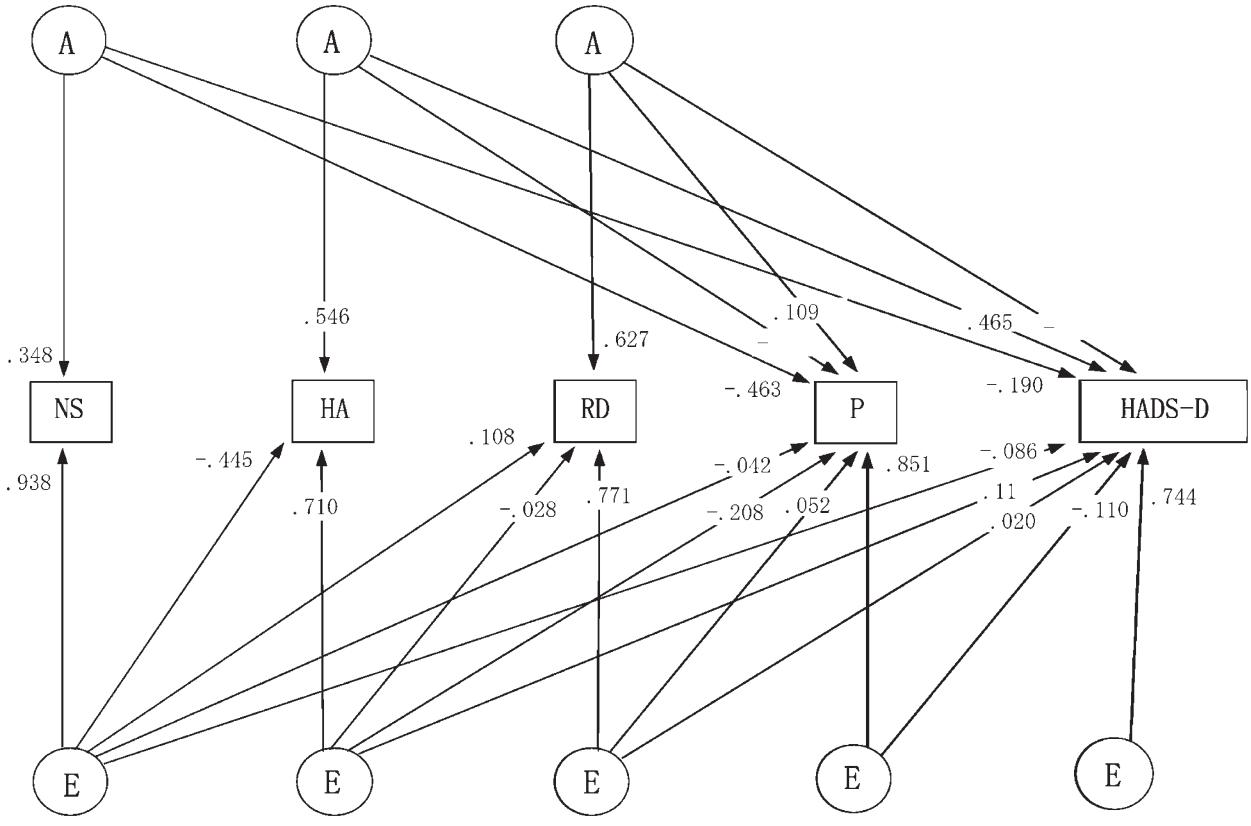

Figure 1 Genetic structure of four temperaments and depression. A, Additive genetic; E, nonshared environment.

which was −226.00, this model improved fitness significantly. Deleting the nonsignificant paths under the three-factor model, the three-specific-factor model was compared which assumed that three latent genetic factors corresponding to NS, HA, and RD are mutually independent. This model fits best. Figure 1 illustrates the best fit picture of the genetic structure of the four dimensions of temperament and depression.

Kendler and associates[6] conducted a longitudinal study to clarify the relationship of personality to major depression and found that while neuroticism is a major part of the diathesis for major depression, still another genetic factor is specific to the depressive disorder. Our findings on mild depression also indicate that depression is genetically influenced but not genetically unique. The three dimensions of temperament of NS, HA, and RD are formulated under the considerable influence of additive genetic effects, and behind depression and the four temperament dimensions of NS, HA, RD, and P, there were three independent genetic factors which corresponded to the tri-dimensional temperament factors (NS, HA, and RD) that Cloninger originally postulated.[21] The mutual independence among these tri-dimensional temperament factors was verified.[22] Although depression is a symptom distinct from dimensions of temperament, it appeared to be largely dependent on the effects of the same gene groups which determine differences among the dimensions of temperament of NS, HA, and RD. Among three genetic groups, the effect of genetic factors related to HA was strongest.

Regarding the effects of environment, our findings suggest that expressions of depression are affected by environmental factors specific to depression which are not shared with the dimensions of temperament. We could find no evidence that environmental experiences shared by other family members, such as common family environment or social influences, are important. A similar finding was reported by Jardine *et al*.[3]

Considering that differences between people on these measures can be explained by differences in both their genes and their environmental experiences, we could hypothesize that dimensions of temperament are closely associated with vulnerability to depressive symptoms, and that the cause of mild depression lay in the interaction between constitutional and experimental factors. These findings also suggest that it might be more heuristic to look for genetic markers for dimensions of temperament rather than for depression.

We could not find a gender difference in the heritability of liability for both dimensions of temperament and mild depression that might suggest similar genetic effects on liability to mild depression in males and females. Although this finding contradicts evidence that the risk of depression in women is greater than that in men, similar findings have been reported in the heritability of major depression.[1,23] These findings suggest that men and women share most genetic influences for not only major depression but also mild depression.

Some limitations of this study should be noted. First, we used self-report questionnaires to measure depression, anxiety, and dimensions of temperament. Although the validity and reliability of these instruments have been established, there are still differences between the results from questionnaires and those from semi-structured interviews. Furthermore, we acknowledge that our sample represents subjects with only moderate to mild depression. Finally, because our sample consists of a young population, further study is needed to clarify whether these results are also applicable to other generations.

Despite these limitations, it should be underscored that depression is affected by additive genetic effects that affect dimensions of temperament together with environmental experiences unique to the individual.

Methods

The data reported here were obtained from twins who participated in the Keio Twin Project (KTP) launched to conduct comprehensive research into human behavioral genetics concerning cognitive abilities and molecular genetics as well as personality in the Japanese population.[24]

The data were collected for 2 successive years. In the first year, the invitations to participate in our project were sent to about 2000 twin pairs in the KTP ranging from 15 to 27 years of age. The letter informed them of the project requirements, a 1-h questionnaire at home and a 3-h assessment on cognitive tasks, personality inventory and blood sampling at the University. Three hundred and fifteen pairs of twins agreed to participate in the research, of whom 263 pairs answered the questionnaire at home and 240 pairs underwent the assessment. All the subjects received a written explanation of the purpose of the study, the research points, confidentiality, and the right to withdraw from the study at any time. Informed consent was obtained from all participants. Subjects under 20 years were also required to get their parents' consent.

Because of the lack of an adequate sample of males, we sent invitations again the next year to the (mostly male) twins of the KTP who did not participate during the previous year. The final sample size was 201 pairs: 89 female and 32 male MZ pairs (MZf and MZm), 36 female DZ and 19 male DZ pairs (DZf and DZm), and 25 opposite sex pairs (DZo). Zygosity was determined from the questionnaires based upon the twins' physical resemblance[25] and the results of the polymorphism of the D4 dopamine receptor and serotonin transporter genes. The average ages were 20.7 ($\pm$3.3) for women and 19.5 ($\pm$3.0) for men.

The participating twin groups were 12% of the original list of potential participants, and there was remarkable inconsistency in sample size for both zygosity and sex. The largest number was obtained from MZf, whereas the DZm sample size was the smallest (just 15% of MZf's). This inconsistency of sample size occurred partially because the Japanese DZ birth rate is still the lowest in the world,[26] and because females are more cooperative toward this kind of scientific research than males, although this sampling skew can be seen in general.

Individual differences in temperament and character were assessed by a Japanese version of Cloninger's Temperament and Character Inventory (TCI). The TCI is a 226-item, true-false questionnaire measuring seven dimensions of personality. Kijima and associates[14] applied the Japanese version of TCI to three student groups. Their findings supported the reliability and validity of the instruments by showing the high internal consistency coefficients and low correlations with the scores of minor psychiatric symptoms. A factor analysis of the data resulted in factor loading patterns similar to those reported by Cloninger and associates.[18]

The subjects were concurrently administered other questionnaires, including the Hospital Anxiety and Depression Scale (HADS).[15,16] HADS is a 14-item self-report screening scale that was originally developed to indicate the possible presence of anxiety and depressive states in the setting of a medical outpatient clinic. Kugaya *et al*[19] applied the Japanese version of HADS to Japanese cancer patients and reported that it is a sensitive and specific tool to screen for psychological distress.

TCI items, questions regarding zygosity diagnosis, and HADS were merged into a booklet and mailed to the subjects. The twin subjects were told to respond to the questionnaire independently without discussing or sharing their responses with one another.

Descriptive statistics including means and SDs of the temperament scores of TCI and the depression score of HADS were computed by SPSS (version 10). To analyze the genetic and environmental contributions to phenotypic variations, univariate and multivariate genetic analyses were conducted. Univariate genetic analysis partitions covariance of twins' phenotypic values into variables based on four basic parameters in terms of a standard behavioral genetics paradigm: additive genetic (A), nonadditive genetic (D), shared environment (C), and nonshared environment (E) factors. An additive genetic factor is the total effect of multiple genes that affect a certain quantitative trait in an additive way. A nonadditive genetic factor is an interactional effect of genotypes at a single gene locus (dominance) or in multiple loci (epistasis). A shared environment is the environmental effect that makes family members seem alike. On the other hand, a nonshared environmental component includes both unique environmental effects and measurement error.

To clarify which parameters contribute to a specific dimension of phenotype, the following four systematic combinations of these four parameters were compared in terms of goodness-of-fit statistics. They are the ACE, ADE, AE, and CE models. The ACE model is the model in which phenotypic covariances are explained only by additive genetic (A), shared environment (C), or nonshared environment (E). ADE, AE, and CE models also stand for the specific combinations of parameters to explain such phenotypic covariances. Each model

contains two submodels: a general and a sex-limitation model. In the sex-limitation model, the equation coefficients were set differently for men and women (am ≠ af, cm ≠ cf, etc). A comparison of fitness of models conducted by maximum likelihood estimation using EQS enabled us to choose the best among the eight possible models.

Multivariate genetic analysis was conducted to clarify the underlying genetic and environmental structures of each personality dimension. The purpose of the multivariate genetic analysis was to check whether there is genetic mediation of environmental overlap between different phenotypes. The first step in examining the genetic and environmental covariations was the Cholesky decomposition which transforms the phenotypic covariance matrices into a moment of two symmetrical matrices. The Cholesky solution can yield genetic and environmental covariances and correlations underlying the phenotypic correlation. The purpose of this analysis is to determine the overall genetic and environmental overlaps between those five personality factors; the no-sex AE model was also considered for E.

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