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Anxiety Proneness Linked to Epistatic Loci in Genome Scan of Human Personality Traits

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A genome-wide scan between normal human personality traits and a set of genetic markers at an average interval of 13 centimorgans was carried out in 758 pairs of siblings in 177 nuclear families of alcoholics. Personality traits were measured by the Tridimensional Personality Questionnaire. We detected significant linkage between the trait Harm Avoidance, a measure of anxiety proneness, and a locus on chromosome 8p21–23 that explained 38% of the trait variance. There was significant evidence of epistasis between the locus on 8p and others on chromosomes 18p, 20p, and 21q. These oligogenic interactions explained most of the variance in Harm Avoidance. There was suggestive evidence of epistasis in other personality traits. These results confirm the important influence of epistasis on human personality suggested by twin and adoption studies. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 81:313–317, 1998. © 1998 Wiley-Liss, Inc.

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INTRODUCTION

Studies of twins and adoptees have identified four quantitative dimensions of personality that are each moderately heritable and stable throughout life, regardless of culture or ethnicity [Loehlin, 1982; Cloninger et al., 1993; Stallings et al., 1996]. These heritable dimensions involve automatic regulatory responses to basic emotional stimuli: fear, anger, disgust, and tenacity. Recently, individual differences in the traits related to fear [Lesch et al., 1996; Ricketts et al., in press] and to anger [Ebstein et al., 1996; Benjamin et al., 1996; Cloninger et al., 1996] were associated with specific gene polymorphisms, each accounting for about 4% of the total variance in the measured trait.

Large-scale studies of personality traits are feasible because they can be quantitatively and reliably measured by self-reports in questionnaires, which agree strongly with reports by spouses and expert raters [Cloninger et al., 1994]. According to a widely used test [Stallings et al., 1996; Ebstein et al., 1996; Howard et al., 1997] called the Tridimensional Personality Questionnaire (TPQ), the four heritable dimensions of personality are Harm Avoidance (anxiety-proneness vs. risk-taking), Novelty Seeking (impulsivity vs. slowness to anger), Reward Dependence (social attachment vs. disgust), and Persistence (tenacity vs. irresolution) [Cloninger et al., 1994]. Furthermore, according to twin studies, each of these four traits is influenced by different sets of genes, thereby providing a test of the specificity of any observed genetic linkage [Heath et al., 1994; Stallings et al., 1996; Cloninger et al., 1996; Svrakic et al., 1996].

Monozygotic twins resemble one another in these personality traits much more than do dizygotic twins, providing estimates of heritability between 40–60% [Heath et al., 1994; Stallings et al., 1996]. However, the resemblance in personality of biological parents and

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their adopted-away children as adults gives consistently lower estimates of heritability (20–30%) [Loehlin et al., 1985; Loehlin, 1992; Plomin et al., 1998]. This difference suggests that within-family environmental effect, dominance (i.e., nonadditive interaction between alleles at a locus), or epistasis (i.e., nonadditive interaction between loci) may account for much of the resemblance in the personalities of monozygotic twins, who are identical at all their loci. Dominance is unlikely because correlations do not differ between personality traits in sibling pairs and parent/offspring pairs [Plomin et al., 1998; Loehlin, 1992]. Epistasis, rather than environmental effect, is the most likely explanation of the discrepancy in heritability estimates for personality traits between adoption and twin studies, because the correlations for personality traits in dizygotic twins are usually less than half the corresponding correlation in monozygotic twins, whether twins are reared together or apart, according to recent reviews of available studies using a wide range of assessment instruments [Henderson, 1982; Loehlin, 1992; Finkel and McGue, 1997; Plomin et al., 1998].

A gene on chromosome 17 regulating the production of the serotonin transporter has been associated with individual differences in Harm Avoidance, accounting for about 4% of its total variation [Lesch et al., 1996; Ricketts et al., 1997]. Likewise, a polymorphism of the D4 dopamine receptor gene (D4DR) on the short arm of chromosome 11 has been found to account for about 4% of the total variation in Novelty Seeking [Ebstein et al., 1996; Benjamin et al., 1996]. These associations have been independently replicated, but not consistently [Goldman, 1996; Cloninger, 1998]; such inconsistency is expected when the effect of each locus depends on other polymorphic loci that may vary between samples [Cloninger, 1997]. In 1989, a large national study known as the Collaborative Study on the Genetics of Alcoholism (COGA) was implemented to identify genetic loci linked with susceptibility to develop alcoholism [Bucholz et al., 1994; Begleiter et al., 1995]. Personality traits, electroencephalographic and event-related potential data [Begleiter et al., 1998], and alcohol-related diagnoses [Reich et al., 1998] were identified as heritable traits predictive of risk of alcoholism. The families selected for study were chosen for a high density of alcoholism and without regard to their personality traits [Bucholz et al., 1994]. Alcoholics scored higher in Harm Avoidance and Novelty Seeking, and lower in Reward Dependence, than nonalcoholics on average, but the variances and correlational architecture of the four TPQ personality dimensions were as expected in a random sample from the general population [Cloninger et al., 1994].

In view of the large number of possible candidate genes for any behavioral trait [Goldman, 1996] and the probable importance of epistasis for personality traits [Finkel and McGue, 1997; Plomin et al., 1998], we carried out a genome-wide scan to detect linkage between the four heritable dimensions of personality measured by the TPQ and polymorphic markers on each human chromosome. To control the experiment-wide error rate, we restricted our analyses to those reported here. We planned all our linkage tests to examine first Harm Avoidance, second Reward Dependence, third Novelty Seeking, and finally Persistence because this was the rank order of their estimated narrow heritability in this sample. Loci suggestive of linkage in this panel will next be tested for replicability in a second panel.

MATERIALS AND METHODS

A whole-genome screen was conducted using 291 microsatellite markers with an average heterozygosity of 0.72. Genotyping was carried out on 987 individuals in 105 pedigrees, including 758 sib pairs in 177 nuclear families. Over 90% of the sib pairs had genotypic data on at least one parent, and approximately 60% had data on both parents.

Genotyping was performed by manual methods (incorporation of radioactivity during PCR amplification and detection of allele sizes by denaturing gel electrophoresis), or by semiautomated methods (fluorescent labeling and detection on the ABI Model 373 DNA sequencer with Genescan and Genotyper software). Data were assessed for non-Mendelian inheritance, questionable data were reexamined, and any remaining inconsistencies were removed within each family. All genotyping and error checking were performed blind to the phenotypes.

We tested for quantitative trait loci (QTLs) using multipoint variance component analysis, which estimates the genetic variance attributable to the region around a genetic marker [Blangero and Almay, 1996]. This method has been used to map genes contributing to the risk for noninsulin-dependent diabetes [Stern et al., 1996] and obesity [Duggirala et al., 1996]. QTLs were detected and variance components were analyzed using an integrated set of computer programs called Sequential Oligogenic Linkage Analysis Routines (SOLAR) [Blangero and Almay, 1996]. Allele frequency estimates were obtained using the maximum likelihood method, as implemented in USERM13 [Boehnke, 1991]. The marker order distances were calculated from these data using CRIMAP [Green et al., 1990]. Maximum likelihood estimates of the identity-by-descent probability matrices for each nuclear family were evaluated using MAPMAKER/SIBS [Kruglyak and Lander, 1995].

Finally, genome-wide significance levels were estimated by empirical simulation of multipoint genome scans using our marker set, sample, and exact test procedures in one-locus quantitative trait linkage analysis. We estimated the statistic n, which is the expected number per genome scan of lod scores that are equal to or greater than the particular observed lod score. This statistic was estimated with our genetic marker set in the scanned sample from approximately 10,000 simulated trials. The evidence of linkage is considered significant when the observed lod score is expected to occur less often than once in 20 such genome scans ($n < .05$). The evidence is suggestive of linkage when the observed lod score would be expected no more than once per genome scan ($n \leq 1$). Comparing the nominal probability of the lod without genome-wide correction to the standardized probability of the lod in our genome

TABLE I. One-Locus Quantitative Trait Analysis*

Trait	Locus	h^2_m	lod	P	Expected n
Harm Avoidance	8:17	0.38	3.2	6×10^{-5}	0.014
	11:194	0.32	1.6	0.003	0.648
	18:109	0.36	1.6	0.004	0.697
Reward Dependence	2:4	0.27	1.7	0.003	0.508
	11:90	0.27	1.5	0.004	0.827
Novelty Seeking	10:88	0.25	1.4	0.005	1.000

*Locus indicates the chromosome and distance in centimorgans from the marker closest to the tip of the short arm, h^2_m indicates the estimate of heritability attributable to the locus and the last three columns give the observed lod score, its nominal significance level (P) without correction for multiple tests in the scan, and the expected number (n) of times a lod score equal or greater is expected to occur per genome scan.

scan with 291 markers and correlated multipoint tests at 1-cM intervals involved about 200 independent comparisons. Thus, an approximate scalar correction of the significance level for two-locus tests in our genome-wide scan can be obtained by multiplying the estimated probability level of the individual observations by 400 (i.e., by 200 for each of the two loci).

RESULTS

We first tested each of the four personality dimensions for linkage to individual points at 1-cM intervals across all chromosomes. This allowed detection of any locus whose average effects influenced a trait regardless of interactions with other loci. Possible QTLs with lod scores of 1.4 or greater, which have a genome-wide probability suggestive of linkage ($n \leq 1$), are shown in Table I. One QTL accounts for 38% of the total variance in Harm Avoidance and gives significant evidence for linkage (lod = 3.2, $P = 0.00006$). The statistic n, which is the expected number of lod scores per genome scan equal to or greater than that observed, was empirically estimated as 0.014. In other words, a lod score of 3.2 or greater is expected to occur only once in 71 genome scans, using our marker and data set. This locus on chromosome 8 is near marker D8S1106, which is located around 8p21–23. It is designated as locus 8:17 because it is about 17 cM centromeric from our marker nearest the tip of the short arm of that chromosome. No other individual locus had significant evidence for linkage to any personality trait.

Next we tested for pairs of loci with effects that add up to influence a quantitative trait. To minimize the number of possible comparisons, we fixed the first locus as the one with the largest lod score for each trait, as shown in Table I. Then we tested for joint linkage of the quantitative trait with the fixed locus and any other point at 1-cM intervals across all chromosomes [Blangero and Almay, 1996]. In Table II we show only those loci whose joint additive effects significantly improved the evidence for linkage beyond that obtained with the first locus alone, as assessed by the nominal P values for the lod conditioned on the first locus (designated as the improvement P). Even when corrected conservatively for 400 independent tests to select the pair, the genome-wide probabilities of the joint lods remain significant for Harm Avoidance, but not for other traits. For Harm Avoidance and the locus on 8:17, the joint lod score increased to 4.0 with 11:192 (near marker D11S1327) and to 3.8 with loci at 8:128 (near GATA12B06) or 20:0 (near D20S448). With the restrictive assumption of additive loci, the increase in lod scores from 3.2 to about 4.0 was not dramatic.

Finally, we tested for pairs of epistatic loci that might have been overlooked in prior analyses [Frankel and Schork, 1996]. We fixed the first locus as in the prior analysis. Allowance for epistasis revealed strong evidence for linkage (lod score 5.1, $P = 7 \times 10^{-6}$) between Harm Avoidance and a pair of loci on chromosomes 8p and 21q (Table III). For this lod score, a conservative estimate of P^*, the expected probability of a lod score equal to or greater than that observed, given the number of degrees of freedom in the model and corrected for the effective number of independent tests in the genome scan, is $P^* = 0.003$. The latter site on chromosome 21q is near marker D21S1440, located in the cytogenetic region 21q21–22.1.

The partitioning of the heritable variance into additive and epistatic components was imprecise. For example, the estimate of the epistatic variance of Harm Avoidance attributable to loci on 8p and 21q (57%) had a large standard error (18%). Also, the epistatic variances attributed to each pair of loci were not independent, and may reflect contributions from several loci influencing each trait. Consequently, each pair of epistatic loci appears to explain about the same variance in each trait (45–66%), which corresponds to the broad heritabilities of the traits in twin studies [Heath et al., 1994; Stallings et al., 1996].

There was suggestive evidence of epistatic contributions to the other three personality traits. Possible in-

TABLE II. Two-Locus Additive Quantitative Trait Analysis†

	Locus 1		Locus 2		Joint two-locus		Improvement
Trait	Locus	h^2_m	Locus	h^2_m	lod	P^*	P
HA	8:17	0.31	8:128	0.13	3.8	0.020	0.05
	8:17	0.30	11:192	0.14	4.0	0.012	0.03
	8:17	0.32	20:0	0.11	3.8	0.024	0.05
RD	2:4	0.18	9:0	0.14	2.2	0.800	0.07

†Locus indicates chromosome and distance, h^2_m indicates estimate of heritability attributable to each locus, and next two columns give the joint two-locus lod score and significance level. Last column gives improvement of the two-locus analysis over the one-locus analysis. HA, Harm Avoidance; RD, Reward Dependence.

*Expected probability of a lod score equal to or greater than that observed, given the number of degrees of freedom in the model and corrected for the effective number of independent tests in the genome scan, which is conservatively estimated here as 400.

TABLE III. Two-Locus Epistatic Quantitative Trait Analysis†

	Locus 1		Locus 2			Joint two-locus		Improvement
Trait	Locus	h^2_m	Locus	h^2_m	h^2_{AA}	lod	P*	P
HA	8:17	0.24	18:20	0.00	0.33	4.4	0.012	0.02
	8:17	0.20	20:0	0.00	0.34	4.6	0.008	0.02
	8:17	0.09	21:62	0.00	0.57	5.1	0.003	0.005
RD	2:4	0.15	1:276	0.00	0.27	2.5	0.800	0.06
	2:4	0.00	2:67	0.00	0.53	3.2	0.200	0.01
	2:4	0.00	2:116	0.00	0.53	3.6	0.080	0.005
	2:4	0.05	9:0	0.00	0.47	2.9	0.400	0.02
	2:4	0.00	11:83	0.00	0.51	3.4	0.120	0.008
	2:4	0.00	16:15	0.00	0.50	3.4	0.160	0.008
	2:4	0.10	19:63	0.00	0.33	2.6	0.800	0.05
NS	10:88	0.00	6:222	0.00	0.54	2.7	0.800	0.02
	10:88	0.00	15:65	0.00	0.50	2.8	0.400	0.02
PS	2:158	0.00	3:220	0.00	0.45	2.5	0.800	0.01

†Locus indicates chromosome and distance, h^2_m indicates estimate of heritability attributable to locus 1 and locus 2 on average alone, h^2_{AA} is the estimate of the epistatic additive by additive interaction, and next two columns give the joint two-locus lod score and significance level. Last column gives improvement of the two-locus epistatic analysis over the one-locus analysis. HA, Harm Avoidance; RD, Reward Dependence; NS, Novelty Seeking; PS, Persistence.
*Expected probability of a lod score equal to or greater than that observed, given the number of degrees of freedom in the model and corrected for the effective number of independent tests in the genome scan, which is conservatively estimated here as 400.

teractions in which the improvement P was less than 0.10 are listed in Table III, to provide a basis for future replication efforts. Each of the four personality traits had evidence of linkage to different sets of epistatic loci, with little or no overlap in linked loci among the four traits.

DISCUSSION

These results provided strong evidence that a genetic locus on 8p21–23, in the vicinity of marker D8S1106, accounts for most of the additive genetic variance (20–30%) in Harm Avoidance in this sample. Epistatic interactions with other genes on chromosome 21q21–22.1, and possibly 18p and 20p, explain most of the total variance in Harm Avoidance (54–66%) and nearly all of its heritable variance.

Genome-wide scans like ours are most helpful in detecting sets of epistatic genes or individual genes with moderately large effects. Such scans may be insensitive to smaller contributions that may be detectable by association with a specific candidate gene. We plan to type additional flanking markers and candidate genes in the regions identified as promising in this initial linkage scan, such as genes for the 5HT3 serotonin receptor on 11q23 and the kainate-sensitive subunit of glutamate receptor 5 on 21q22.1. This glutamate receptor subtype is primarily expressed in the CA3 region of the hippocampus, which has crucial interactions with serotonin receptors in the regulation of anxiety and related behaviors such as trembling [Isaacson and Lanthorn, 1981].

Human chromosome 8p21–23 is homologous to mouse chromosomal region 8:10–30. This region has been linked to individual differences in sensitization by repeated ethanol exposure [Phillips et al., 1995] and initial sensitivity to ataxia by ethanol [Gallaher et al., 1996] in recombinant inbred strains of mice. Such homology is especially interesting because Harm Avoidance is associated with individual differences in sensitivity to aversive stimulation [Corr et al., 1995; Cloninger, 1998]. This sensitivity makes anxiety proneness (i.e., high Harm Avoidance) an important risk factor for many forms of psychopathology, including alcoholism [Cloninger et al., 1995], mood disorders [Svrakic et al., 1996], and psychoses [Cloninger et al., 1994]. There is also replicated evidence of linkage of susceptibility to schizophrenia to the region of 8p21–23 [Pulver et al., 1995; Cloninger, 1997].

Overall, our results suggest that individual differences in human personality depend to a large extent on nonadditive interactions among several polymorphic loci. Each of the four heritable personality traits appears to be linked to different sets of epistatic loci, with little or no overlap in loci among these sets. Our identification of a few genes with moderately large average effects on anxiety proneness may lead to a clearer understanding of the complex neurobiology of the development of personality and its disorders. The evidence for epistatic effects of loci on 8p and 21q on Harm Avoidance appears strongly significant, even after correction for multiple tests in a genome-wide scan.

However, the possible contributions to other traits are only suggestive in genome-wide significance. Furthermore, the experiment-wide probability of false-positive linkage becomes progressively higher than genome-wide significance as we move from Harm Avoidance to Reward Dependence, then to Novelty Seeking, and finally Persistence. The findings observed for Novelty Seeking and Persistence may be chance observations when the number of prior traits tested is taken into account for experiment-wide significance; based on heritability estimates, we planned to test for linkage first with Harm Avoidance, second with Reward De-

pendence, third with Novelty Seeking, and fourth with Persistence. There is little experience in detecting epistatic interactions by linkage analysis of human traits, even though epistasis is likely to be important for oligogenic traits. Therefore, our findings need to be replicated in other samples to evaluate the reproducibility of our findings and to assist in the ongoing development of better procedures for linkage detection with complex human traits.

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