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Personality and polymorphisms of genes involved in aminergic neurotransmission

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Abstract

Genetic factors significantly contribute to the determination of human personality traits assessed by self-report questionnaires. However, only in the past few years have common genetic polymorphisms especially the dopamine D4 receptor and the serotonin transporter promoter region been associated with specific personality traits such as novelty seeking and harm avoidance, respectively. The effects of these genes are modest and several genes are likely accounting for individual differences in personality dimensions that can be attributed to genetic factors. Molecular genetic studies of adult personality have also been extended to investigations of early human temperament and some of the genes associated with adult personality traits are also contributing to the earliest developmental expressions of human behavior. Additionally, some of these same genes have also been implicated in various types of abnormal behavior including addiction, obsessive–compulsive disorder, attention deficit, depression, aggression and psychosis. Future research directions will no doubt take advantage of the bioinformatics revolution coinciding with the completion of the first phase of the human genome project. It should soon be possible to identify many of the genes contributing to specific personality traits and to better define their role in determining normal and abnormal behavior from early development through adulthood.

Keywords: Personality; Genes; Neurotransmission; Polymorphism; Temperament; Abnormal behavior

1. Definition and measurement of personality

Personality is the characteristic manner or style of an individual's behavior as opposed to the goals towards which it is directed (motivation), or the machinery of its execution (cognitive and motor skills). Personality refers to the vigor, temper or persistence of behavior or to the emotional expression that accompanies it, such as fearfulness, exuberance, aggressiveness, or self-restraint (Loehlin, 1992). Many other definitions of personality exist but most genetic studies are based on this definition. The vast majority of genetic research on personality involves self-report questionnaires administered to adolescents and adults. People's responses to such questions are remarkably stable, even over several decades (Costa and McCrae, 1997).

A number of self-report questionnaires are in use and they appear to measure similar facets of personality. Self-report personality inventories include the Revised NEO Personality Inventory (NEO-PI-R) (McCrae and Costa, 1997), Eysenck's Personality Inventory (Eysenck, 1952), Zuckerman's Sensation Seeking Scale (Zuckerman, 1994), Cattell's 16 PF (Cattell, 1946) and Cloninger's Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987) and Temperament Character Index (TCI) (Cloninger et al., 1993). Formulas can be used to convert NEO-PI-R scores into TPQ Harm Avoidance and Novelty Seeking, illustrating the inter-relatedness of these questionnaires (Benjamin et al., 1996). To summarize, all the major self-report questionnaires appear to reliably measure many of the same personality factors especially the higher categories of Novelty Seeking (extraversion, conscientiousness, sensation seeking, psychoticism) and Harm Avoidance (neuroticism, anxiety-related traits).

One questionnaire that we have found particularly useful and has proven heuristic value in our studies is Cloninger's TPQ (Cloninger, 1987). The TPQ is a 100

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question instrument that requires a yes/no answer. Most subjects complete the form in about a half-hour. Questions relating to Novelty Seeking include the following:

- I often try new things just for fun or thrills, even if most people think it is a waste of time (Yes)
- I often do things based on how I feel at the moment without thinking about how they were done in the past (Yes)
- I am much more controlled than most people (No)

Questions relating to Harm Avoidance include the following:

- I usually am confident that everything will go well, even in situations that worry most people (No)
- I often feel tense and worried in unfamiliar in unfamiliar situations, even when others feel there is no danger at all (Yes)
- I often have to stop what I'm doing because I start worrying about what might go wrong (Yes)

The TPQ draws on human and animal work to suggest that behavior is mediated by certain neurotransmitters, which underlie three basic and largely heritable dimensions, called "Novelty Seeking", "Harm Avoidance" and "Reward Dependence". In populations who filled out NEO and TPQ questionnaires, TPQ Harm Avoidance was highly correlated with NEO Neuroticism, and Novelty Seeking was positively correlated with Extraversion and negatively correlated with Conscientiousness. Novelty Seeking therefore taps aspects of impulsiveness, curiosity (or exploratory behavior in animals) and disorderliness. Reward Dependence is the TPQ term for attachment to others, sentimentality and warmth; its opposites are pragmatism and tough-mindedness.

According to the biological theory behind the TPQ, Harm Avoidance is the inhibition of approach behaviors, and the enhancement of escape behaviors, and these are principally served by the serotonin (5-HT) system in most animals. The trait has face-valid resemblance to human neuroticism and perhaps depression. Novelty Seeking, the increased tendency to respond with approach to novel and promising situations, is principally served by the mesolimbic dopamine system. Rewarding activities, including certain drugs, increase dopamine release or inhibit its reuptake in this system (Schultz, 1997). Reward Dependence reflects the persistence of behavior that is likely to be intermittently, rather than immediately, rewarded, so that a key sub-scale of Reward Dependence in the TPQ is Persistence.

2. Heritability of personality traits

Twin studies demonstrate that personality traits measured by self-report questionnaires show moderate heritability and secondly, although environmental influence is also important almost all the environmental variance is non-shared (Loehlin, 1992). Heritabilities in the 30–50% range are typical. Extraversion is one of the most highly heritable categories ($\sim$ 50%) closely followed by neuroticism or emotional stability ($\sim$ 40%).

3. Association of personality traits with specific genes

3.1. Dopamine D4 receptor

Only recently has an association between a specific genetic polymorphism and a specific personality trait been reported (Benjamin et al., 1996; Ebstein et al., 1996). Our seminal study catalyzed many investigations by others and ourselves aimed at validating these first reports and identifying other genes that contribute to personality factors.

These two initial studies examined the role of the exon III 48 bp repeat dopamine D4 receptor polymorphism in personality. This gene has a highly polymorphic 16 amino acid repeat region in the putative third cytoplasmic loop that varies between 2 and 10 repeats in most populations and changes the length of the receptor protein (Van Tol, 1996; Lichter et al., 1993). There is some evidence that the long and short forms of this protein have a moderate functional significance (Asghari et al., 1994, 1995), although a more recent study showed that the polymorphic region of the loop does not appear to affect the specificity or efficiency of G(i)alpha coupling (Kazmi et al., 2000). Two approaches were used. The Israeli study was a case-control design, whereas the NIH group's sample also included a number of sib pairs allowing for both a between- and a within-families design. Both studies suggested an association between novelty seeking and the long alleles of the dopamine D4 receptor (DRD4). Although some subsequent studies confirmed our initial findings (Kuhn et al., 1999; Noble et al., 1998; Strobel et al., 1999; Tomitaka et al., 1999), others did not (Bau et al., 1999; Gelernter et al., 1997; Jonsson et al., 1998; Pogue-Geile et al., 1998; Sander et al., 1997a; Sullivan et al., 1998; Vandenbergh et al., 1997b).

We note, however, that three recent studies appear to confirm the relevancy of the DRD4 gene to novelty seeking. A Japanese group has characterized several polymorphisms in the upstream promoter region of the DRD4 gene and one of these was associated with higher novelty seeking scores in a group of Japanese subjects (Okuyama et al., 2000). This particular promoter region polymorphism is functionally significant and the T variant of the C-521T polymorphism reduces transcriptional efficiency. In a second study, a Finnish group has shown an association between the DRD4 exon III 2 and 5 repeat alleles and high novelty seeking scores in a very large and homogeneous Finnish birth cohort of more than 4700 subjects (Ekelund et al., 1999). Both of these studies suggest that

our original observation of an association between the DRD4 48 bp repeat region and TPQ novelty seeking may have been due to linkage disequilibrium between this polymorphism and another polymorphism within the DRD4 gene (the promoter region?) or in a neighboring gene. Finally, the first genome-wide scan in personality genetics in a group of alcoholic families (Cloninger et al., 1998), which reported a linkage between anxiety-related traits and a region on chr 8p, also observed a linkage between novelty seeking and the region on chr 11 where the DRD4 gene is located (Cloninger, personal communication). This finding is currently being replicated in the second panel from this cohort.

Mutant mice lacking the DRD4 receptor also provide some evidence for a novelty seeking connection and this gene. In addition to increased sensitivity to ethanol (Rubinstein et al., 1997), these mice also exhibit reduced behavioral response to novel stimuli (Dulawa et al., 1999). The DRD4 receptor has also been analyzed in dog breeds and the long D allele was dominant in the endogenous Japanese breed (Shiba) compared to Golden retriever (Niimi et al., 1999). It is interesting that the Shiba is considered an aggressive species and some kinds of aggression are associated with sensation/novelty seeking personality traits in humans (Zuckerman, 1994).

3.2. Serotonin transporter promoter region polymorphism (5-HTTLPR)

Following our report of an association between DRD4 and novelty seeking, Lesch et al. showed an association between a newly discovered 44 bp deletion in the promoter region of the serotonin transporter promoter region (5-HTTLPR) affecting transcription of the gene (Heils et al., 1996) and associated with neuroticism or HA personality traits (Lesch et al., 1996). Some subsequent reports replicated the initial association (Greenberg et al., 1999; Katsuragi et al., 1999; Murakami et al., 1999; Ricketts et al., 1998; Osher et al., 2000) whereas two yielded ambiguous results (Gelernter et al., 1998; Mazzanti et al., 1998). Several studies failed to observe any association between anxiety related traits and the 5-HTTLPR polymorphism (Ball et al., 1997; Flory et al., 1999; Ebstein et al., 1997a; Gustavsson et al., 1999; Hamilton et al., 1999; Jorm et al., 1998; Kumakiri et al., 1999; Deary et al., 1999).

Two studies (Lerman et al., 2000; Hu et al., 2000) found a relationship between the personality trait of neuroticism and the 5-HTTLPR short genotypes and smoking behavior. Other studies found an association between a dopamine transporter polymorphism (SLC6A3-9), smoking status and Novelty Seeking (Lerman et al., 1999; Sabol et al., 1999). However, Jorm et al. (2000) in a sample of over 800 subjects found no evidence for an association between either the 5-HTTLPR or dopamine transporter (DAT) polymorphism on smoking behavior or personality traits.

3.3. Other polymorphisms and personality traits

Another dopamine receptor that has been examined for a role in personality traits is the dopamine 3 receptor (DRD3). In a large sample of Caucasians (Henderson et al., 2000), those in the first half of the split sample with at least one of the DRD3 Ser(9) alleles had significantly higher scores in neuroticism ($p = 0.006$) and behavioral inhibition ($p = 0.003$). There was a trend, failing to meet the 1% significance criterion, for those with this genotype also to have higher depression and anxiety. However, when the second half of the split sample was analyzed, the results failed to obtain significance. Another group of investigators found that alcohol dependent patients with the genotype A1/A2 showed significantly higher novelty seeking scores than patients with the genotype A1/A1. An association between the DRD3 receptor and novelty seeking was observed in a small group of bipolar patients (Staner et al., 1998). Also in a group of bipolar patients, Harm Avoidance was associated with the serotonergic 5-HT_{2a} receptor polymorphism (Blairy et al., 2000).

4. Gene interactions

Certain rare genetic disorders are caused by single gene mutations. Whether the mode of inheritance is recessive, dominant, or X-linked, these disorders are called simple, or Mendelian. However, common diseases are influenced (not "caused") by more than one gene, and by environment. For such traits, the contribution of any single gene may be very small and any one gene may be neither necessary nor sufficient for the determination of the phentoype. Discovering the genes involved is therefore more difficult, and these disorders are called "complex". Quantitative phenotypes with approximately normal distributions, like height and intelligence, also display complex genetics, and this is also true of personality.

As soon as more than one gene is involved in the determining of the phenotype, the concept of "epistasis", or gene–gene interactions, also becomes important. The effect of a single gene may depend radically on the simultaneous presence or absence of another gene or genes. The word "radically" distinguishes this situation from simple, so-called "additive" effects of two or more genes, where each gene contributes incrementally to the phenotype. A good analogy is provided by a hand of cards in a card game. A two of clubs or diamonds may be a worthless card, but 2 twos (a "pair" in poker) is worth more than twice as much as one ("synergism"). The same two of clubs in a game of bridge, even when clubs are trumps, will be of little value early in the game; however, when another suit is called for, *provided the player has no cards of that suit*, he or she can play the two of clubs and win (negative interaction with the other suit and synergistic

interaction with the contract stipulating clubs as trumps). The main point about epistasis, then, is that the leading actor in the drama is not a single gene, but a particular genetic *combination.*

Recent studies in personality genetics are now revealing the role of multiple gene effects in the determination of this complex phenotype.

Noble et al. (1998) observed an interaction between the DRD4 and DRD2 polymorphisms on Novelty Seeking. Novelty Seeking was significantly higher in boys having, in common, all three minor (A1, B1, and Intron 6 1) alleles of the DRD2 compared to boys without any of these alleles. Boys with the DRD4 7 repeat (7R) allele also had a significantly higher Novelty Seeking score than those without this allele. However, the greatest difference in Novelty Seeking score was found when boys having all three minor DRD2 alleles and the DRD4 7R allele were contrasted to those without any of these alleles. Neither the DRD2 nor the DRD4 polymorphisms differentiated total Harm Avoidance score.

Two groups (Ebstein et al., 1997b; Kuhn et al., 1999) observed an interaction between the serotonin 5-HT_{2c} receptor polymorphism and the DRD4 polymorphism on TPQ reward dependent behavior. Our studied showed that when present in the same individual, the 5-HT_{2c} and dopamine receptor polymorphisms account for 30% of the observed variance for persistence (RD2) and 13% of the variance for reward dependence scores (RD134).

Our group also examined the role of three functional polymorphisms: DRD4, 5-HTTLPR serotonin transporter and catechol-*o*-methyltransferase polymorphisms, for association with TPQ personality factors in 455 subjects (Benjamin et al., 2000b). In the absence of the short 5-HTTLPR allele and in the presence of the high enzyme activity, catechol-*o*-methyltransferase val/val genotype, novelty seeking scores are higher in the presence of the DRD4 7 repeat allele (Fig. 1). The effect of these three polymorphisms on novelty seeking was also examined using a within-families design. Siblings who shared identical genotype groups for all three polymorphisms (catechol-*o*-methyltransferase, DRD4 and 5-HTTLPR) had significantly correlated Novelty Seeking scores whereas sibs with dissimilar genotypes in at least one polymorphism showed no significant correlation for Novelty Seeking scores. Similar interactions were also observed between these three polymorphisms and Novelty Seeking when the 150 independently recruited and non-related subjects were analyzed. We also observed an interaction between the catechol-*o*-methyltransferase and 5-HTTLPR polymorphisms and TPQ Persistence scores (Benjamin et al., 2000b). Subjects with high Persistence scores are characterized as industrious, hard-working, ambitious, perfectionist.

We note that only a handful of additional common polymorphisms have been examined for association with personality traits including the transcription factor AP-2beta gene (Damberg et al., 2000), the α_{2A} adenoreceptor (Comings et al., 2000) and a tyrosine hydroxylase TCAT repeat (Persson et al., 2000). In a Brazilian study of male alcoholics, an association was observed between the TAQ A1 dopamine D2 receptor polymorphism and TPQ Harm Avoidance personality traits, stress related traits and facets of alcoholism (Bau et al., 2000).

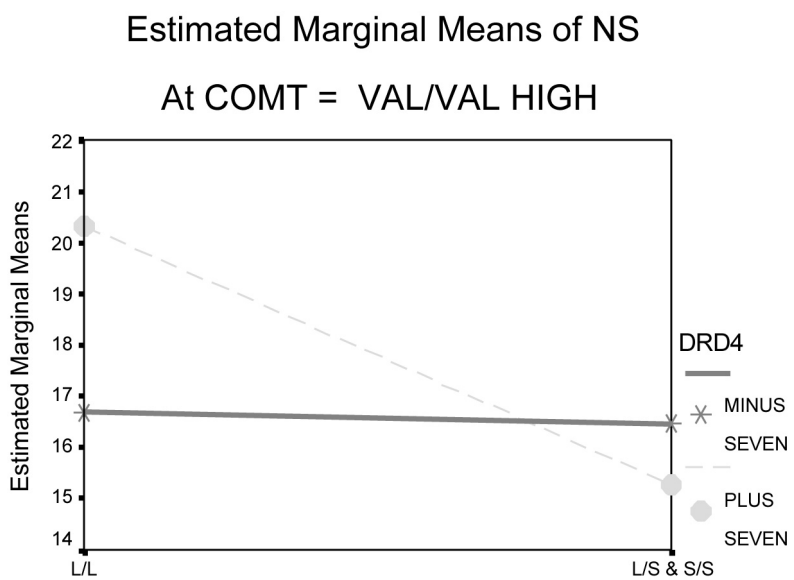

Fig. 1. TPQ novelty seeking scores in the presence of three polymorphisms: DRD4, catechol-*o*-methyltransferase and 5-HTTLPR (Benjamin et al., 2000a). All subjects represented were homozygous for the high enzyme activity catechol-*o*-methyltransferase val/val genotype. The *Y* axis = TPQ novelty seeking scores. Subjects at the left *Y* axis are homozygous for the long/long 5-HTTLPR genotype whereas subjects at the right *Y* axis carry at least one short 5-HTTLPR allele (the so-called "neuroticism" allele). Note the relatively large difference in mean novelty seeking scores between subjects with the DRD4 7 repeat allele and subjects without the 7 repeat in the absence of the short 5-HTTLPR allele.

5. Extension of genetic personality studies to infant temperament

Individual differences in temperament, i.e., individual differences in emotional, motoric, and attentional reactivity, are apparent from the first days of life. One of the most widely used methods to assess temperament in the first weeks of life is the Neonatal Behavioral Assessment Scale (NBAS) (Brazelton and Brazelton, 1995). The NBAS assesses the behavioral repertoire of infants from birth to 1 month. It attempts to capture individual differences in the complexity of behavioral responses to environmental stimuli as the neonate moves from sleep states to alert states to crying states.

In a first study of its kind (Ebstein et al., 1998), we examined the role of two common polymorphisms on neonatal behavior, evaluated at 2 weeks of age, in 81 neonates (40 males and 41 females) using the NBAS. We also note that this initial investigation is the first in a longitudinal study of neonate, infant and toddler behavior that we have initiated.

The effect of the DRD4 short (s) vs. DRD4 long (l) and 5-HTTLPR short/short (s/s) vs. 5-HTTLPR long/short (l/s) and long/long (l/l) on four of the NBAS temperament clusters was compared by multivariate analysis. A significant association of DRD4 across the NBAS clusters was observed. Univariate *F* tests showed significant effects of DRD4 on all four of the temperament clusters. Overall, the presence of the long forms of the DRD4 exon III repeat region is to raise the mean score for all four of the temperament clusters.

No direct effect of 5-HTTLPR was observed by either multivariate or univariate *F* tests on any of the temperament clusters. However, a significant multivariate interaction was observed between DRD4 and 5-HTTLPR and univariate *F* tests showed a significant interaction between the two polymorphisms on orientation (Fig. 2). The effect size of DRD4 on orientation was much larger in those neonates homozygous for the short (s/s) 5-HTTLPR genotype compared to infants with either the s/l or l/l genotypes. Moreover, no significant effect of L-DRD4 on orientation was observed in neonates grouped by the 5-HTTLPR l/l or l/s, whereas the effect of L-DRD4 repeat alleles was significant in neonates with the s/s 5-HTTLPR genotype. The effect of 5-HTTLPR (s/s) was to lower the orientation score for the group of neonates lacking the L-DRD4.

In summary, the results indicate that infants with one or more long alleles of 5-HTTLPR, which is associated with less anxious traits in adults, show no further enhancing effect of the long DRD4 alleles, which also promote approach-type behaviors in adults. However, in infants with the inhibiting form (at least in adults) of 5-HTTLPR, long DRD4 alleles, but not short DRD4 alleles, oppose this inhibition.

We also examined the association of DRD4 and 5-HTTLPR and temperament in 76 two-month old infants (39 boys and 37 girls) who had participated in the neonatal

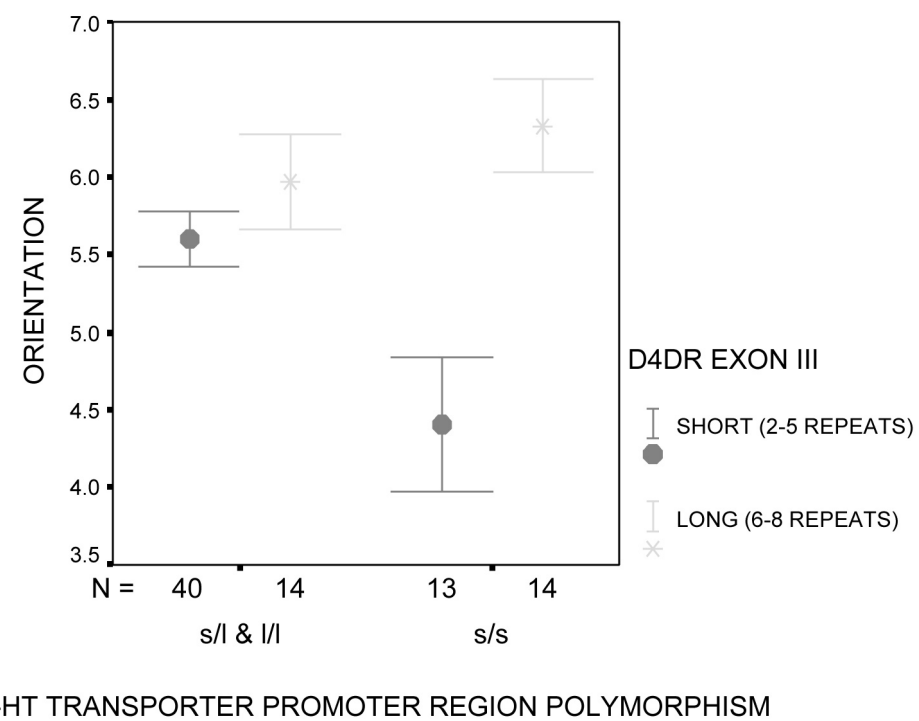

Fig. 2. NBAS orientation scores in 2-week-old infants sorted by the dopamine D4 receptor exon II repeat polymorphism (DRD4) and the serotonin transporter promoter region polymorphism (5-HTTLPR) (Ebstein et al., 1998). Error bars represent mean values ± SEM. The effect size of DRD4 on orientation was much larger in those neonates homozygous for the short (s/s) 5-HTTLPR genotype compared to infants with either the s/l or l/l genotypes ($\partial\eta^2$: 0.35 vs. 0.02).

assessment described above (Auerbach et al., 1999). Mothers completed the IBQ (Rothbart, 1986). IBQ scores reflect the ease of elicitation of a given reaction and the intensity of that reaction. Both the stability and validity of the IBQ have been documented (Rothbart, 1986; Worobey and Blajda, 1989).

Temperament stability was examined by calculating bivariate correlation coefficients for the NBAS and the IBQ scales. There were significant negative correlations between several of the NBAS and the IBQ scales.

We next considered the effect of the DRD4 and 5-HTTLPR genotypes on the IBQ scales. Infants with long DRD4 alleles had significantly lower scores on Negative Emotionality and Distress to Limitations than infants with the short DRD4 alleles. In contrast, infants with the s/s 5-HTTLPR genotype had higher scores on Negative Emotionality and Distress to Limitations than infants with the l/s or l/l genotypes. A DRD4 main effect of Distress to Sudden or Novel Stimuli approached significance. Infants with the long DRD4 alleles were less distressed by sudden or novel stimuli than were infants with the short alleles. In those infants lacking the DRD4 long repeat alleles, the effect of the short homozygous form (s/s) of the 5-HTTLPR gene on Negative Emotionality and Distress to Limitations was significant, whereas no effect of this polymorphism was observed in infants possessing the long DRD4 alleles. In the absence of the long form of the DRD4 allele, the effect of the s/s form of 5-HTTLPR gene was to significantly raise the scores for Negative Emotionality and Distress to Limitations.

6. Pleiotropic effects of common polymorphisms affecting human behavior

Not surprisingly, three of the genes most intensely investigated in personality genetics, DRD4, 5-HTTLPR and catechol-*o*-methyltransferase, are known to affect a wide range of human behaviors. One of the most robust findings is the reported association between the 7 repeat allele and attention deficit hyperactivity disorder a heterogeneous childhood disruptive behavior characterized by impulsive acts. It is interesting to note that adults diagnosed with attention deficit hyperactivity disorder show higher TPQ novelty seeking and HA scores (Downey et al., 1997). Many (Comings et al., 1999; Faraone et al., 1999; LaHoste et al., 1996; Rowe et al., 1998; Smalley et al., 1998; Swanson et al., 1998; Swanson et al., 2000) but not all (Castellanos et al., 1998; Eisenberg et al., 2000; Hawi et al., 2000; Kotler et al., 1999) studies show an association between attention deficit hyperactivity disorder and the DRD4 7 repeat.

The DRD4 polymorphism has also been shown in some studies to be associated with addictive behavior. We note that substance abusers including both alcoholics (Cloninger et al., 1995) and heroin addicts (Mel et al., 1998) are distinguished by high TPQ novelty seeking scores. We observed in a case-control design an association between heroin addicts and the DRD4 7 repeat (Kotler et al., 1997, Mel et al., 1998), which has also been observed in a Chinese population (Li et al., 1997). Goldman et al. (1997) observed linkage between alcoholism in American Indians and the region on chromosome 11 very close to the DRD4 gene. Also a Japanese study (Muramatsu et al., 1996) observed an interaction between the DRD4 receptor and alcoholism in subjects carrying the ALDH2(2) protective 'flushing' allele, common in some Asiatic populations.

The 5-HTTLPR polymorphism has been associated in some studies with obsessive–compulsive disorder (McDougle et al., 1998; Bengel et al., 1999), in depression and anxiety in Parkinson's disease (Menza et al., 1999), in alcoholism (Sander et al., 1997b; Ishiguro et al., 1999; Hallikainen et al., 1999), compulsive buying (Devor et al., 1999), autism (Persico et al., 2000; Yirmiya et al., 2000; Klauck et al., 1997; Cook et al., 1997) and bipolar disorder (Furlong et al., 1998).

The catechol-*o*-methyltransferase high/low enzyme activity val/met polymorphism has also been examined in a number of human behaviors. Two groups including ourselves found an association between the low enzyme activity met allele and violent behavior in schizophrenia (Lachman et al., 1998; Strous et al., 1997; Kotler et al., 1999). The association between the high enzyme val allele and heroin addiction first reported by Vandenbergh et al. (1997a) was recently confirmed by us in a family-based design (Horowitz et al., 2000). We (Alsobrook II et al., 2000) also confirmed an association between this polymorphism and obsessive–compulsive disorder (Karayiorgou et al., 1997, 1999). Finally, we note that we have observed a provisional association between the catechol-*o*-methyltransferase polymorphism and hypnotizability (Lichtenberg et al., 2000).

A common theme underlying the pleiotropic affects of these three genes might be their role in modulating neurotransmitter systems underpinning similar facets of higher cortical and limbic functions subsumed under the heading of Executive Function. These three genes appear to regulate aspects of impulsiveness and attention-processes that are common to normal personality as well as disturbances reflected in such diverse disorders as autism, attention deficit hyperactivity disorder, schizophrenia and addiction.

7. Future directions

Finding genes contributing to human personality reflects the challenges encountered in genetic analysis of other complex human traits including type II diabetes (Alper, 2000), obesity (Arner, 2000), schizophrenia and bipolar disorder (Gershon, 2000), hypertension (Garbers and Dubois, 1999) and allergies (Ono, 2000), to name just a few areas of active research. Small effect size of individ-

ual genes and oligogenic interactions confound attempts to establish the role of common polymorphisms in contributing to these complex disorders.

As pointed out by Risch in a recent review (Risch, 2000), the molecular methods used successfully to identify the genes underlying rare Mendelian syndromes are failing to find the numerous genes causing more common, familial, non-Mendelian diseases. However, there is room for optimism especially with the completion of the human genome sequence. New opportunities are being presented for unraveling the complex genetic basis of non-Mendelian disorders based on large-scale genome-wide studies.

In the past few years in the field of personality, common genetic polymorphisms have been identified that contribute to the determination of personality traits determined by self-report questionnaires. Although the importance of genetic factors in determining human temperament has been recognized for two decades, recognition was lacking regarding the possibility that the revolution in molecular biology could also be applied to the mystery of human personality. Recent studies initially focused on a candidate gene approach to personality and some common polymorphisms were associated with specific personality dimensions. This new field took an important turn with the first publication by Cloninger et al. (1998) of a genome wide scan for chromosomal regions harboring genes contributing to the determination of human temperament. Not unexpectedly, it was almost immediately apparent that 'personality' genes have a modest effect size and that several genes are likely contributing to any specific personality traits (Ebstein et al., 1997a; Kuhn et al., 1999; Cloninger et al., 1998; Noble et al., 1998; Benjamin et al., 2000a,b). A particularly exciting development is the possibility that the role of genes in human temperament could be recognized very early in development at a time when environmental influences are minimum (Auerbach et al., 1999; Ebstein et al., 1998). Finally, there is increasing awareness of the role played by personality factors in psychopathology and the possibility that personality may be a useful endophenotype in analyzing the genetics of mental illness.

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References

Alper, J., 2000. New insights into Type 2 diabetes. Science 289, 37–39.

Alsobrook, J.P. II, Zohar, A.H., Leboyer, M., Chabane, N., Ebstein, R.P., Paul, D.L., 2000. Association between the COMT locus and obsessive compulsive disorder in females but not males. Neuropsychiatr. Genet. in press.

Arner, P., 2000. Obesity—a genetic disease of adipose tissue? Br. J. Nutr. 83 (Suppl. 1), S9–S16.

Asghari, V., Schoots, O., van Kats, S., Ohara, K., Jovanovic, V., Guan, H.C., Bunzow, J.R., Petronis, A., Van Tol, H.H., 1994. Dopamine D4 receptor repeat: analysis of different native and mutant forms of the human and rat genes. Mol. Pharmacol. 46, 364–373.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., Van Tol, H.H., 1995. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J. Neurochem. 65, 1157–1165.

Auerbach, J., Geller, V., Lezer, S., Shinwell, E., Belmaker, R.H., Levine, J., Ebstein, R., 1999. Dopamine D4 receptor (D4DR) and serotonin transporter promoter (5-HTTLPR) polymorphisms in the determination of temperament in 2-month-old infants. Mol. Psychiatry 4, 369–373.

Ball, D., Hill, L., Freeman, B., Eley, T.C., Strelau, J., Riemann, R., Spinath, F.M., Angleitner, A., Plomin, R., 1997. The serotonin transporter gene and peer-rated neuroticism. NeuroReport 8, 1301–1304.

Bau, C.H., Roman, T., Almeida, S., Hutz, M.H., 1999. Dopamine D4 receptor gene and personality dimensions in Brazilian male alcoholics. Psychiatr. Genet. 9, 139–143.

Bau, C.H., Almeida, S., Hutz, M.H., 2000. The TaqI A1 allele of the dopamine D2 receptor gene and alcoholism in Brazil: association and interaction with stress and harm avoidance on severity prediction. Am. J. Med. Genet. 96, 302–306.

Bengel, D., Greenberg, B., Cora-Locatelli, G., Altemus, M., Heils, A., Li, Q., Murphy, D., 1999. Association of the serotonin transporter promoter regulatory region polymorphism and obsessive compulsive disorder. Mol. Psychiatry 4, 463–466.

Benjamin, J., Li, L., Patterson, C., Greenberg, B.D., Murphy, D.L., Hamer, D.H., 1996. Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. Nat. Genet. 12, 81–84.

Benjamin, J., Osher, Y., Kotler, M., Gritsenko, I., Nemanov, L., Belmaker, R.H., Ebstein, R.P., 2000a. Association between tridimensional personality questionnaire (TPQ) traits and three functional polymorphisms: dopamine receptor (D4) (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol-*o*-methyltransferase (COMT). Mol. Psychiatry 5, 96–100.

Benjamin, J., Osher, Y., Lichtenberg, P., Bachner-Melman, R., Gritsenko, I., Kotler, M., Belmaker, R.H., Valsky, V., Drendel, M., Ebstein, R.P., 2000b. An interaction between the catechol-*o*-methyltransferase and serotonin transporter promoter region polymorphisms contributes to tridimensional personality questionnaire persistence scores in normal subjects. Neuropsychobiology 41, 48–53.

Blairy, S., Massat, I., Staner, L., Le Bon, O., Van Gestel, S., Van Broeckhoven, C., Hilger, C., Hentges, F., Souery, D., Mendlewicz, J., 2000. 5-HT2a receptor polymorphism gene in bipolar disorder and harm avoidance personality trait (in process citation). Am. J. Med. Genet. 96, 360–364.

Brazelton, T.B.N., Brazelton, J.K., 1995. Neonatal Behavior Assessment Scale. MacKeith Press, London.

Castellanos, F.X. et al., 1998. Lack of an association between a dopamine-4 receptor polymorphism and attention-deficit/hyperactivity disorder: genetic and brain morphometric analyses [see comments]. Mol. Psychiatry 3, 431–434.

Cattell, R.B., 1946. Description and Measurement of Personality. World, Yonkers-on-Hudson.

Cloninger, C.R., 1987. A systematic method for clinical description and classification of personality variants. A proposal. Arch. Gen. Psychiatry 44, 573–588.

Cloninger, C.R., Svrakic, D.M., Przybeck, T.R., 1993. A psychobiological model of temperament and character. Arch. Gen. Psychiatry 50, 975–990.

Cloninger, C.R., Sigvardsson, S., Przybeck, T.R., Svrakic, D.M., 1995. Personality antecendents of alcoholism in a national area probability sample. Eur. Arch. Psychiatry Clin. Neurosci. 245, 239–244.

Cloninger, C.R., Van Eerdewegh, P., Goate, A., Edenberg, H.J., Blangero, J., Hesselbrock, V., Reich, T., Nurnberger, J. Jr., Schuckit, M., Porjesz, B., Crowe, R., Rice, J.P., Foroud, T., Przybeck, T.R., Almasy, L., Bucholz, K., Wu, W., Shears, S., Carr, K., Crose, C., Willig, C., Zhao, J., Tischfield, J.A., Li, T.K., Conneally, P.M. et al., 1998. Anxiety proneness linked to epistatic loci in genome scan of human personality traits. Am. J. Med. Genet. 81, 313–317.

Comings, D.E., Gonzalez, N., Wu, S., Gade, R., Muhleman, D., Saucier, G., Johnson, P., Verde, R., Rosenthal, R.J., Lesieur, H.R., Rugle, L.J., Miller, W.B., MacMurray, J.P., 1999. Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. Am. J. Med. Genet. 88, 358.

Comings, D.E., Johnson, J.P., Gonzalez, N.S., Huss, M., Saucier, G., McGue, M., MacMurray, J., 2000. Association between the adrenergic alpha 2A receptor gene (ADRA2A) and measures of irritability, hostility, impulsivity and memory in normal subjects (in process citation). Psychiatr. Genet. 10, 39–42.

Cook, E.H. Jr., Courchesne, R., Lord, C., Cox, N.J., Yan, S., Lincoln, A., Haas, R., Courchesne, E., Leventhal, B.L., 1997. Evidence of linkage between the serotonin transporter and autistic disorder. Mol. Psychiatry 2, 247–250.

Costa, P.T. Jr., McCrae, R.R., 1997. Stability and change in personality assessment: the revised NEO personality inventory in the year 2000. J. Pers. Assess. 68, 86–94.

Damberg, M., Garpenstrand, H., Alfredsson, J., Ekblom, J., Forslund, K., Rylander, G., Oreland, L., 2000. A polymorphic region in the human transcription factor AP-2beta gene is associated with specific personality traits (in process citation). Mol. Psychiatry 5, 220–224.

Deary, I.J., Battersby, S., Whiteman, M.C., Connor, J.M., Fowkes, F.G., Harmar, A., 1999. Neuroticism and polymorphisms in the serotonin transporter gene. Psychol. Med. 29, 735–739.

Devor, E.J., Magee, H.J., Dill-Devor, R.M., Gabel, J., Black, D.W., 1999. Serotonin transporter gene (5-HTT) polymorphisms and compulsive buying. Am. J. Med. Genet. 88, 123–125.

Downey, K.K., Stelson, F.W., Pomerleau, O.F., Giordani, B., 1997. Adult attention deficit hyperactivity disorder: psychological test profiles in a clinical population. J. Nerv. Ment. Dis. 185, 32–38.

Dulawa, S.C., Grandy, D.K., Low, M.J., Paulus, M.P., Geyer, M.A., 1999. Dopamine D4 receptor-knock-out mice exhibit reduced exploration of novel stimuli. J. Neurosci. 19, 9550–9556.

Ebstein, R.P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., Bennett, E.R., Nemanov, L., Katz, M., Belmaker, R.H., 1996. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. Nat. Genet. 12, 78–80.

Ebstein, R.P., Gritsenko, I., Nemanov, L., Frisch, A., Osher, Y., Belmaker, R.H., 1997a. No association between the serotonin transporter gene regulatory region polymorphism and the tridimensional personality questionnaire (TPQ) temperament of harm avoidance. Mol. Psychiatry 2, 224–226.

Ebstein, R.P., Segman, R., Benjamin, J., Osher, Y., Nemanov, L., Belmaker, R.H., 1997b. 5-HT2C (HTR2C) serotonin receptor gene polymorphisms associated with the human personality trait of reward dependence: interaction with dopamine D4 receptor (D4DR) and dopamine D3 receptor (D3DR) polymorphisms. Am. J. Med. Genet. 74, 65.

Ebstein, R.P., Levine, J., Geller, V., Auerbach, J., Gritsenko, I., Belmaker, R.H., 1998. Dopamine D4 receptor and serotonin transporter promoter in the determination of neonatal temperament. Mol. Psychiatry 3, 238–246.

Eisenberg, J., Zohar, A., Mei-Tal, G., Steinberg, A., Tartakovsky, E., Gritsenko, I., Nemanov, L., Ebstein, R.P., 2000. A haplotype relative risk study of the dopamine D4 receptor (DRD4) exon III repeat polymorphism and attention deficit hyperactivity disorder (ADHD). Am. J. Med. Genet. 96, 258.

Ekelund, J., Lichtermann, D., Jarvelin, M.R., Peltonen, L., 1999. Association between novelty seeking and the type 4 dopamine receptor gene in a large Finnish cohort sample. Am. J. Psychiatry 156, 1453–1455.

Eysenck, H.J., 1952. The scientific study of personality. Routledge and Kegan Paul, London.

Faraone, S.V., Biederman, J., Weiffenbach, B., Keith, T., Chu, M.P., Weaver, A., Spencer, T.J., Wilens, T.E., Frazier, J., Cleves, M., Sakai, J., 1999. Dopamine D4 gene 7-repeat allele and attention deficit hyperactivity disorder. Am. J. Psychiat. 156, 768.

Flory, J.D., Manuck, S.B., Ferrell, R.E., Dent, K.M., Peters, D.G., Muldoon, M.F., 1999. Neuroticism is not associcated with the serotonin promoter (5-HTTLPR) polymorphism. Mol. Psychiatry 4, 93–96.

Furlong, R.A., Ho, L., Walsh, C., Rubinsztein, J.S., Jain, S., Paykel, E.S., Easton, D., Rubinsztein, D.C., 1998. Analysis and meta-analysis of two serotonin transporter gene polymorphisms in bipolar and unipolar affective disorders (in process citation). Am. J. Med. Genet. 81, 58–63.

Garbers, D.L., Dubois, S.K., 1999. The molecular basis of hypertension. Annu. Rev. Biochem. 68, 127–155.

Gelernter, J., Kranzler, H., Coccaro, E., Siever, L., New, A., Mulgrew, C.L., 1997. D4 dopamine-receptor (DRD4) alleles and novelty seeking in substance-dependent personality disorder, and control subjects. Am. J. Hum. Genet. 61, 1144–1152.

Gelernter, J., Kranzler, H., Coccaro, E.F., Siever, L.J., New, A.S., 1998. Serotonin transporter protein gene polymorphism and personality measures in African American and European American subjects. Am. J. Psychiatry 155, 1332–1338.

Gershon, E.S., 2000. Bipolar illness and schizophrenia as oligogenic diseases: implications for the future. Biol. Psychiatry 47, 240–244.

Goldman, D., Knowler, W.C., Hanson, R.L., Robin, R.W., Urbanek, M., Moore, E., Bennett, P.H., Long, J., 1997. Autosome-wide scan for alcohol dependence in southwestern American Indians provides suggestive evidence for loci on chromosomes 4 and 11. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 74, 574–575.

Greenberg, B.D., Tolliver, T.J., Huang, S.J., Li, Q., Bengel, D., Murphy, D.L., 1999. Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. Am. J. Med. Genet. 88, 83–87.

Gustavsson, J.P., Nothen, M.M., Jonsson, E.G., Neidt, H., Forslund, K., Rylander, G., Mattila-Evenden, M., Sedvall, G.C., Propping, P., Asberg, M., 1999. No association between serotonin transporter gene polymorphisms and personality traits. Neuropsychiatr. Genet. submitted.

Hallikainen, T., Saito, T., Lachman, H.M., Volavka, J., Pohjalainen, T., Ryynanen, O.P., Kauhanen, J., Syvalahti, E., Hietala, J., Tiihonen, J., 1999. Association between low activity serotonin promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Mol. Psychiatry 4, 385–388.

Hamilton, S.P., Heiman, G.A., Haghighi, F., Mick, S., Klein, D.F., Hodge, S.E., Weissman, M.M., Fyer, A.J., Knowles, J.A., 1999. Lack of genetic linkage or association between a functional serotonin transporter polymorphism and panic disorder. Psychiatr. Genet. 9, 1–6.

Hawi, Z. et al., 2000. No association of the dopamine DRD4 receptor (DRD4) gene polymorphism with attention deficit hyperactivity disorder (ADHD) in the Irish population. Am. J. Med. Genet., Neuropsychiatr. Genet. 96, 268–272.

Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., Lesch, K.P., 1996. Allelic variation of human serotonin transporter gene expression. J. Neurochem. 66, 2621–2624.

Henderson, A.S., Korten, A.E., Jorm, A.F., Jacomb, P.A., Christensen, H., Rodgers, B., Tan, X., Easteal, S., 2000. COMT and DRD3 polymorphisms, environmental exposures and personality traits related to common mental discorders. Am. J. Med. Genet. 96, 102–107.

Horowitz, R., Shufman, A., Aharoni, S., Kotler, M., Ebstein, R.P., 2000. Confirmation of an excess of the high enzyme activity COMT val allele in heroin addicts in a familty-based haplotype relative risk study. Am. J. Med. Genet. (Neuropsychiatr. Genet.), in press.

Hu, S., Brody, C.L., Fisher, C., Gunzerath, L., Nelson, M.L., Sabol, S.Z., Sirota, L.A., Marcus, S.E., Greenberg, B.D., Murphy, D.L., Hamer, D.H., 2000. Interaction between the serotonin transporter gene and neuroticism in cigarette smoking behavior. Mol. Psychiatry 5, 181–188.

Ishiguro, H., Saito, T., Akazawa, S., Mitushio, H., Tada, K., Enomoto, M., Mifune, H., Toru, M., Shibuya, H., Arinami, T., 1999. Association between drinking-related antisocial behavior and a polymorphism in the serotonin transporter gene in a Japanese population. Alcohol. Clin. Exp. Res. 23, 1281–1284.

Jonsson, E.G., Nothen, M.M., Gustavsson, J.P., Neidt, H., Forslund, K., Mattila-Evenden, M., Rylander, G., Propping, P., Asberg, M., 1998. Lack of association between dopamine D4 receptor gene and personality traits. Psychol. Med. 28, 985–989.

Jorm, A.F., Henderson, A.S., Jacomb, P.A., Christensen, H., Korten, A.E., Rodgers, B., Tan, X., Easteal, S., 1998. An association study of a functional polymorphism of the serotonin transporter gene with personality and psychiatric symptoms. Mol. Psychiatry 3, 449–451.

Jorm, A.F., Henderson, A.S., Jacomb, P.A., Christensen, H., Korten, A.E., Rodgers, B., Tan, X., Easteal, S., 2000. Association of smoking and personality with a polymorphism of the dopamine transporter gene: results from a community survey. Am. J. Med. Genet. 96, 331–334.

Karayiorgou, M., Altemus, M., Galke, B.L., Goldman, D., Murphy, D.L., Ott, J., Gogos, J.A., 1997. Genotype determining low catechol-*o*-methyltransferase activity as a risk factor for obsessive–compulsive disorder. Proc. Natl. Acad. Sci. U. S. A. 94, 4572–4575.

Karayiorgou, M., Sobin, C., Blundell, M.L., Galke, B.L., Malinova, L., Goldberg, P., Ott, J., Gogos, J.A., 1999. Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessive–compulsive disorder. Biol. Psychiatry 45, 1178–1189.

Katsuragi, S., Kunugi, H., Sano, A., Tsutsumi, T., Isogawa, K., Nanko, S., Akiyoshi, J., 1999. Association between serotonin transporter gene polymorphism and anxiety related traits. Biol. Psychiatry 45, 368–370.

Kazmi, M.A., Snyder, L.A., Cypess, A.M., Graber, S.G., Sakmar, T.P., 2000. Selective reconstitution of human D4 dopamine receptor variants with Gi alpha subtypes. Biochemistry 39, 3734–3744.

Klauck, S.M., Poustka, F., Benner, A., Lesch, K.P., Poustka, A., 1997. Serotonin transporter (5-HTT) gene variants associated with autism? Hum. Mol. Genet. 6, 2233–2238.

Kotler, M., Barak, P., Cohen, H., Averbuch, I.E., Grinshpoon, A., Gritsenko, I., Nemanov, L., Ebstein, R.P., 1999. Homicidal behavior in schizophrenia associated with a genetic polymorphism determining low catechol-*o*-methyltransferase (COMT) activity. Am. J. Med. Genet. 88, 628–633.

Kotler, M., Cohen, H., Segman, R., Gritsenko, I., Nemanov, L., Lerer, B., Kramer, I., Zer-Zion, M., Kletz, I., Ebstein, R.P., 1997. Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. Mol. Psychiatry 2, 251–254.

Kuhn, K.U., Meyer, K., Nothen, M.M., Gansicke, M., Papassotiropoulos, A., Maier, W., 1999. Allelic variants of dopamine receptor D4 (DRD4) and serotonin receptor 5HT2c (HTR2c) and temperament factors: replication tests. Am. J. Med. Genet. 88, 168–172.

Kumakiri, C., Kodama, K., Shimizu, E., Yamanouchi, N., Okada, S., Noda, S., Okamoto, H., Sato, T., Shirasawa, H., 1999. Study of the association between the serotonin transporter gene regulatory region polymorphism and personality traits in a Japanese population. Neurosci. Lett. 263, 205–207.

Lachman, H.M., Nolan, K.A., Mohr, P., Saito, T., Volavka, J., 1998. Association between catechol-*o*-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder. Am. J. Psychiatry 155, 835–837.

LaHoste, G.J. et al., 1996. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol. Psychiatry 1, 121–124.

Lerman, C., Caporaso, N.E., Audrain, J., Main, D., Bowman, E.D., Lockshin, B., Boyd, N.R., Shields, P.G., 1999. Evidence suggesting the role of specific genetic factors in cigartette smoking. Health Psychol. 18, 14–20.

Lerman, C., Caporaso, N.E., Audrain, J., Main, D., Boyd, N.R., Shields, P.G., 2000. Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependence. Mol. Psychiatry 5, 189–192.

Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H., Murphy, D.L., 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274, 1527–1531.

Li, T., Xu, K., Deng, H., Cai, G., Liu, J., Liu, X., Wang, R., Xiang, X., Zhao, J., Murray, R.M., Sham, P.C., Collier, D.A., 1997. Association analysis of the dopamine D4 gene exon III VNTR and heroin abuse in Chinese subjects. Mol. Psychiatry 2, 413–416.

Lichtenberg, P., Bachner-Melman, R., Gritsenko, I., Ebstein, R.P., 2000. An association study between the catechol-*o*-methyltransferase polymorphism and hypnotizability. Neuropsychiatr. Genet. in press.

Lichter, J.B., Barr, C.L., Kennedy, J.L., Van Tol, H.H., Kidd, K.K., Livak, K.J., 1993. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. Hum. Mol. Genet. 2, 767–773.

Loehlin, J.C., 1992. Genes and Environment in Personality Development. Sage, Newbury Park.

Mazzanti, C.M., Lappalainen, J., Long, J.C., Bengel, D., Naukkarinen, H., Eggert, M., Virkkunen, M., Linnoila, M., Goldman, D., 1998. Role of the serotonin transporter promoter polymorphism in anxiety-related traits. Arch. Gen. Psychiatry 55, 936–940.

McCrae, R.R., Costa, P.T. Jr., 1997. Personality trait structure as a human universal. Am. Psychol. 52, 509–516.

McDougle, C.J., Epperson, C.N., Price, L.H., Gelernter, J., 1998. Evidence for linkage disequilibrium between serotonin transporter gene (SLC6A4) and osessive compulsive disorder. Mol. Psychiatry 3, 270–273.

Mel, H., Horowitz, R., Ohel, N., Kramer, I., Kotler, M., Cohen, H., Gritsenko, I., Ebstein, R.P., 1998. Additional evidence for an association between the dopamine D4 receptor (D4DR) exon III seven-repeat allele and substance abuse in opioid dependent subjects: Relationship of treatment retention to genotype and personality. Addict. Biol. 3, 473–481.

Menza, M.A., Palermo, B., DiPaola, R., Sage, J.I., Ricketts, M.H., 1999. Depression and anxiety in Parkinson's disease: possible effect of genetic variation in the serotonin transporter. J. Geriatr. Psychiatry Neurol. 12, 49–52.

Murakami, F., Shimomura, T., Kotani, K., Ikawa, S., Nanba, E., Adachi, K., 1999. Anxiety traits associated with a polymorphism in the serotonin transporter gene regulatory region in the Japanese. J. Hum. Genet. 44, 15–17.

Muramatsu, T., Higuchi, S., Murayama, M., Matsushita, S., Hayashida, M., 1996. Association between alcoholism and the dopamine D4 receptor gene. J. Med. Genet. 33, 113–115.

Niimi, Y., Inoue-Murayama, M., Murayama, Y., Ito, S., Iwasaki, T., 1999. Allelic variation of the D4 dopamine receptor polymorphic region in two dog breeds, Golden Retriever and Shiba. J. Vet. Med. Sci. 61, 1281–1286.

Noble, E.P., Ozkaragoz, T.Z., Ritchie, T.L., Zhang, X., Belin, T.R., Sparkes, R.S., 1998. D2 and D4 dopamine receptor polymorphisms and personality. Am. J. Med. Genet. 81, 257–267.

Okuyama, Y., Ishiguro, H., Nankai, M., Shibuya, H., Watanabe, A., Arinami, T., 2000. Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. Mol. Psychiatry 5, 64–69.

Ono, S.J., 2000. Molecular genetics of allergic diseases. Annu. Rev. Immunol. 18, 347–366.

Osher, Y., Hamer, D., Benjamin, J., 2000. Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israeli sibling pairs. Mol. Psychiatry 5, 216–219.

Persico, A.M., Militerni, R., Bravaccio, C., Schneider, C., Melmed, R., Conciatori, M., Damiani, V., Baldi, A., Keller, F., 2000. Lack of association between serotonin transporter gene promoter variants and autistic disorder in two ethnically disctinct samples. Am. J. Med. Genet. 96, 123–127.

Persson, M., Wasserman, D., Wasserman, E., Wasserman, G.J., Bergman, H., Terenius, L., Gyllander, A., Neiman, J., Geijer, T., 2000. Search for the influence of the tyrosine hydroxylase (TCAT)(n) repeat polymorphism on personality traits. Psychiatry Res. 95, 1–8.

Pogue-Geile, M., Ferrell, R., Deka, R., Debski, T., Manuck, S., 1998. Human novelty seeking personality traits and dopamine D4 receptor polymorphisms: a twin and genetic assocaition study. Am. J. Med. Genet. 81, 44–48.

Ricketts, M.H., Hamer, R.M., Sage, J.I., Manowitz, P., Feng, F., Menza, M.A., 1998. Association of a serotonin transporter gene promoter polymorphism with harm avoidance behaviour in an elderly population. Psychiat. Genet. 8, 41–44.

Risch, N.J., 2000. Searching for genetic determinants in the new milennium. Nature 405, 847–856.

Rothbart, M.K., 1986. Longitudinal observation of infant temperament. Dev. Psychol. 22, 356–365.

Rowe, D.C. et al., 1998. Dopamine DRD4 receptor polymorphism and attention deficit hyperactivity disorder. Mol. Psychiatry 3, 419–426.

Rubinstein, M., Phillips, T.J., Bunzow, J.R., Falzone, T.L., Dziewczapolski, G., Zhang, G., Fang, Y., Larson, J.L., McDougall, J.A., Chester, J.A., Saez, C., Pugsley, T.A., Gershanik, O., Low, M.J., Grandy, D.K., 1997. Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine and methamphetamine. Cell 90, 991–1001.

Sabol, S.Z., Nelson, M.L., Fisher, C., Gunzerath, L., Brody, C.L., Hu, S., Sirota, L.A., Marcus, S.E., Greenberg, B.D., Lucas, F.R.t., Benjamin, J., Murphy, D.L., Hamer, D.H., 1999. A genetic association for cigarette smoking behavior. Health Psychol. 18, 7–13.

Sander, T., Harms, H., Dufeu, P., Kuhn, S., Rommelspacher, H., Schmidt, L.G., 1997a. Dopamine D4 receptor exon III alleles and variation of novelty seeking in alcoholics. Am. J. Med. Genet. 74, 483–487.

Sander, T., Harms, H., Lesch, K.P., Dufeu, P., Kuhn, S., Hoehe, M., Rommelspacher, H., Schmidt, L.G., 1997b. Association analysis of a regulatory variation of the serotonin transporter gene with severe alcohol dependence. Alcohol. Clin. Exp. Res. 21, 1356–1359.

Schultz, W., 1997. Dopamine neurons and their role in reward mechanisms. Curr. Opin. Neurobiol. 7, 191–197.

Smalley, S.L. et al., 1998. Evidence that the dopamine D4 receptor is a susceptibility gene in attention deficit hyperactivity disorder [see comments]. Mol. Psychiatry 3, 427–430.

Staner, L., Hilger, C., Hentges, F., Monreal, J., Hoffmann, A., Couturier, M., Le Bon, O., Stefos, G., Souery, D., Mendlewicz, J., 1998. Association between novelty-seeking and the dopamine D3 receptor gene in bipolar patients: a preliminary report. Am. J. Med. Genet. 81, 192–194.

Strobel, A., Wehr, A., Michel, A., Brocke, B., 1999. Association between the dopamine D4 receptor (DRD4) exon III polymorphism and measures of Novelty Seeking in a German population. Mol. Psychiatry 4, 378–384.

Strous, R.D., Bark, N., Parsia, S.S., Volavka, J., Lachman, H.M., 1997. Analysis of a functional catechol-*o*-methyltransferase gene polymorphism in schizophrenia: evidence for association with aggressive and antisocial behavior. Psychiatry Res. 69, 71–77.

Sullivan, P.F., Fifield, W.J., Kennedy, M.A., Mulder, R.T., Sellman, J.D., Joyce, P.R., 1998. No association between novelty seeking and the type 4 dopamine receptor gene (DRD4) in two New Zealand samples. Am. J. Psychiatry 155, 98–101.

Swanson, J.M. et al., 1998. Association of the dopamine receptor D4 (DRD4) gene with a refined phenotype of attention deficit hyperactivity disorder (ADHD): a family-based approach. Mol. Psychiatry 3, 38–41.

Swanson, J. et al., 2000. Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention [in Processs Citation]. Proc. Natl. Acad. Sci. U. S. A. 97, 4754–4759.

Tomitaka, M., Tomitaka, S., Otuka, Y., Kim, K., Matuki, H., Sakamoto, K., Tanaka, A., 1999. Association between novelty seeking and dopamine receptor (DRD4) exon III polymorphism in Japanese subjects. Am. J. Med. Genet. 88, 469–471.

Van Tol, H.H., 1996. The dopamine D4 receptor. NIDA Res. Monogr. 161, 20–38.

Vandenbergh, D.J., Rodriguez, L.A., Miller, I.T., Uhl, G.R., Lachman, H.M., 1997a. High acitivity catechol-*o*-methyltransferase allele is more prevalent in polysubstance abusers. Am. J. Med. Genet. 74, 439–442.

Vandenbergh, D.J., Zonderman, A.B., Wang, J., Uhl, G.R., Costa, P.T. Jr., 1997b. No association between novelty seeking and dopamine D4 receptor (D4DR) exon III seven repeat alleles in Baltimore Longitudinal Study of Aging Participants. Mol. Psychiatry 2, 417–419.

Worobey, J., Blajda, V.M., 1989. Temperament rayings at 2 weeks, 2 months, and 1 year: Differential stability of activity and emotionality. Dev. Psychol. 25, 257–263.

Yirmiya, N., Pilowsky, T., Nemanov, L., Arbelle, S., Feinsilver, T., Fried, I., Ebstein, R.P., 2000. Analysis of three coding region (dopamine D4 receptor, catechol-*o*-methyltransferase and serotonin transporter region) polymorphisms in autism: evidence for an association with the serotonin transporter. In: Schopler, E., Marcus, L., Shulman, C., Yirmiya, N. (Eds.), The Research Basis of Autism Intervention. Kluwer Academic/Plenum.

Zuckerman, M., 1994. Behavioral Expressions and Biosocial Bases of Sensation Seeking. Cambridge Univ. Press, New York.