

FEATURE REVIEW

The molecular genetic architecture of human personality: beyond self-report questionnaires

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Molecular genetic studies of personality began with two high impact papers in 1996 that showed provisional associations between the dopamine *DRD4* exon III repeat region and Novelty Seeking/Extraversion. These first two reports were shortly followed by an investigation linking Neuroticism/Harm Avoidance with the serotonin transporter (*SLC6A4*) promoter region polymorphism (5-HTTLPR). In the ensuing decade, thousands of subjects have been studied for association between these genes and personality, assessed by using self-report questionnaires, with erratic success in replication of the first findings for Novelty Seeking (*DRD4*) and Harm Avoidance (5-HTTLPR). Small effect sizes characteristic of non-Mendelian traits, polygenic patterns of inheritance and true heterogeneity between studies confound attempts to reach a consensus regarding the role of common polymorphisms in contributing to personality domains. Nevertheless, the current state of personality genetics is far from being bleak. Several new paradigms especially functional neuroimaging or 'imaging genomics' have strengthened the connection between 5-HTTLPR and anxiety-related personality traits. The demonstrations that early environmental information can considerably strengthen and even uncover associations between genes and behavior (Caspi's seminal studies and more recently the demonstration that early environment impacts on *DRD4* and Novelty Seeking) are notable and herald a new era of personality genetics. Finally, consideration of the broader phenotypic expression of common polymorphisms (e.g. the 'social brain', altruism, etc.) and the use of new experimental paradigms including neurophysiological, neuropsychological and computer games that go beyond the narrow self-report questionnaire design will enable a deeper understanding of how common genetic polymorphisms modulate human behavior. Human personality, defined by Webster as the quality or state of being a person or the complex of characteristics that distinguishes an individual, surely requires a more encompassing view towards understanding its complex molecular genetic architecture.

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In the beginning

The auspicious debut of molecular genetic studies of personality began with the simultaneous publication of two articles in *Nature Genetics* in 1996 showing an association between Tridimensional Personality Questionnaire (TPQ)^{1,2} Novelty Seeking³ and NEO-PI-R Extraversion⁴ and the dopamine D4 exon III (D4.7) seven repeat.^{5,6} These two seminal reports were quickly followed by the study of Lesch *et al.*⁷ showing an association between the short *SLC6A4* (serotonin transporter) promoter 44 bp repeat deletion/insertion (5-HTTLPR) and NEO-PI-R Neuroticism.⁸ These reports spurred a continuing series of investigations

that have resulted in both successful and unsuccessful efforts at replicating these first studies. Molecular personality genetics has evidently not escaped the conundrum of non-replication that continues to plague the genetics of complex human phenotypes (see review by Mayeux⁹ in the issue of *J Clin Invest* dedicated to complex disorders). Nevertheless, despite apparent difficulties in confirming first findings, enthusiasm for personality genetic studies continues to wax and not to wane testifying to the allure of this subject for many behavioral scientists. The current review will mainly but not exclusively focus on the two genes, *DRD4* and *SLC6A4*, that have been most studied in association studies of personality genetics.

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Personality constructs: what are they?

Cloninger's TPQ measures are derived from a general biosocial theory of personality.¹ Three dimensions of personality are defined in terms of the basic

stimulus–response characteristics of Novelty Seeking, Harm Avoidance and Reward Dependence. This model of personality represents one of the first attempts to integrate current ideas on neurotransmitter systems into personality research. Novelty Seeking was suggested to be associated with dopamine neurotransmission, Harm Avoidance with serotonin and Reward with norepinephrine. Harm Avoidance involves a heritable bias in the inhibition of behavior in response to signals of punishment and frustrative non-reward. It is observed as pessimistic worry in anticipation of problems, fear of uncertainty, shyness with strangers and rapid fatigability. Novelty Seeking reflects a heritable bias in the initiation or activation of appetitive approach in response to novelty, approach to signals of reward, active avoidance of conditioned signals of punishment and skilled escape from unconditioned punishment. Reward Dependence reflects a heritable bias in the maintenance of behavior in response to cues of social reward. It is observed as sentimentality, social sensitivity, attachment and dependence on approval by others. Individuals high in Reward Dependence are tender-hearted, sensitive, socially dependent and sociable. Subsequently, the TPQ evolved into the TCI² which added an additional three so-called ‘character’ scales to the original four temperament traits.

Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness are the major dimensions of the so-called five-factor model of the NEO and were derived by empirical analyses. The NEO factors are lexical constructs based on trait descriptions in natural language. The revised NEO personality inventory NEO-PI-R⁸ was developed to measure these five personality dimensions. NEO-PI-R Neuroticism includes traits such as anxiety, angry hostility, depression, self-consciousness, impulsiveness and vulnerability. NEO-PI-R Extraversion includes traits such as gregariousness, assertiveness, activity, excitement-seeking and positive emotions. Formulas can be used to convert NEO-PI-R Neuroticism scores into TPQ Harm Avoidance and Novelty Seeking, illustrating the inter-relatedness of these questionnaires.¹⁰

A study by De Fruyt *et al.*¹¹ showed that TPQ (temperament)/TCI scales significantly correlated ($r > 0.4$) with at least one NEO-PI-R domain scale, demonstrating that each TCI scale shows considerable overlap with the Big Five. Harm Avoidance is strongly positively correlated with Neuroticism and negatively related to Extraversion. The scale is further negatively related to Openness and Conscientiousness. Novelty seeking is related to Extraversion and Openness and negatively to Conscientiousness. Persistence is highly correlated with Conscientiousness. Reward dependence primarily relates to Extraversion and secondarily to Openness.

Stallings *et al.*¹² carried out a joint analysis of the factor structure of the EPQ-R,¹³ Gray’s personality dimensions¹⁴ and TPQ personality scales. The factor pattern was consistent with the conceptualization

that Cloninger’s Harm Avoidance and Gray’s Anxiety dimensions are very similar and most likely represent a 45° rotation of Eysenck’s Extraversion and Neuroticism dimensions. However, Cloninger’s Novelty Seeking dimension is not synonymous with Gray’s Impulsivity but appears to be further rotated into Eysenck’s Psychoticism space. Reward also is not equivalent to EPQ Psychoticism, showing only modest negative correlations with this scale.

We examined the factor structure of the TPQ in use in our personality studies.¹⁵ The Hebrew version of the TPQ was administered to 1139 individuals (aged 16–78 years) in the community. Factor analysis was run first on individual items, and then on the 12 subscales described by Cloninger *et al.*¹⁶ The factor analyses were restricted to four orthogonal factors in order to attempt confirmation of the corrected four-factor solution.¹² In the individual item analysis, four orthogonal factors recognizable as Novelty Seeking, Reward Dependence, Harm Avoidance and Persistence emerged. The data were analyzed for sex differences and age effects. Women scored higher than men did on most sub-scales of Harm Avoidance and Reward Dependence. The younger group (up to 21 years of age) scored higher on Novelty Seeking and Reward Dependence and lower on Harm Avoidance than the older group, but no sex by age interaction was detected. Similar results are observed with NEO-PI-R Neuroticism (women score higher than men) and an age-associated decline is observed in Extraversion scores. Comparable results have been observed for other translated versions of the TPQ/TCI.

Interrogation of literature: search method

We employed a Medline search towards a comprehensive survey of the literature using the following terms: (1) Personality AND temperament and found 98 references; (2) Personality AND polymorphism (509 references); (3) Personality AND genes (928 references) and (4) Personality AND Twin (1581 references). We also mined the published meta-analyses of personality genetics and combined all references in a single ENDNOTE[®] file and then eliminated duplicates. From this database, we selected the articles that are discussed in the current review.

Reviews and meta-analyses of personality genetics

The status of personality genetics has been the focus of many reviews^{17–24} as well as the subject of a book.²⁵ Additionally, several meta-analyses have been carried out for *DRD4* (Novelty Seeking/Extraversion) and the serotonin transporter (Harm Avoidance/Neuroticism).^{26–32} A single meta-analysis examined the role of brain-derived neurotrophic factor (BDNF) and Neuroticism.³³ Overall, meta-analyses compiled for self-report questionnaires failed to provide strong evidence that either the *DRD4* D4.7 repeat is significantly contributing to Novelty Seeking or that the

5-HTTLPR short allele is significantly contributes to Neuroticism/Harm Avoidance. The evidence appears stronger for the transporter–Neuroticism association as it does for the association between the *DRD4* C-521T promoter-region single-nucleotide polymorphism (SNP). A cardinal feature of complex phenotypes, small effect size ($d=0.23$ for Neuroticism and 5-HTTLPR;³¹ $d=0.34$ for Novelty Seeking and *DRD4* SNP C-521T;³⁰ where effect size ‘ d ’ was calculated as the difference in personality measure means between genotype groups divided by the pooled standard deviation of the two groups) is likely an important reason for failure to replicate first findings. Subtle differences between studies can easily obscure effect sizes of polymorphisms that only explain a few percent of the variance between subjects. Additionally, as noted in all the meta-analyses, considerable heterogeneity was observed between studies indicating that there is greater variation among outcomes than expected by chance (Figure 1).

Sen *et al.*³² identified the type of questionnaire employed (TPQ vs NEO-PI-R) as a main source of heterogeneity for the trait of Neuroticism/Harm Avoidance. Highly significant results were obtained for the NEO Neuroticism trait and 5-HTTLPR, whereas there was only a nonsignificant association when TPQ Harm Avoidance was used to assess subjects. These results could be attributed to the observation by Jang *et al.*²⁰ who observed as regards Extraversion or Novelty Seeking, that all inventories included sociability and affiliation but not all scales included exhibitionism or optimism. Vis-à-vis Neuroticism or Harm Avoidance, some scales (NEO-PI-R) include impulsivity whereas others do not. Conceivably, a necessary condition required to show positive association between 5-HTTLPR and Neuroticism is that ‘impulsivity’ be included in the anxiety-related personality construct. On the other hand, variables including gender and ethnicity were unlikely to be major contributors to the heterogeneity found by Sen *et al.*³²

The reader is also referred to the interesting papers of Munafo *et al.*^{28,34,35} who examined the impact of publication bias (authors tend to publish only positive results – a tendency encouraged by most journals) and other methodological problems connected with meta-analysis. Munafo *et al.* offered the sound advice that large studies, with sufficient power and employing multiple phenotype measures, is likely the best strategy towards resolving the role of *DRD4* and 5-HTTLPR as well as other genes in partially determining the architecture of personality traits.

Serotonin transporter *SLC6A4*

A large UK study

An ambitious investigation of personality genetics has been reported by Willis-Owen *et al.*²⁷ This study is noteworthy since the authors used a novel and cost-effective recruiting strategy by solely selecting for

genotyping individuals from extremes of the phenotypic distribution of anxiety-related personality traits. In total, 731 unrelated subjects from the 5% tails of the Revised Eysenck Personality Questionnaire¹³ (EPQ-R) were genotyped for 5-HTTLPR. Despite the large sample size, no statistically significant effects of genotype could be identified on either EPQ-Neuroticism or a related phenotype, major depression. The population included in the study showed no evidence for population stratification (see Pritchard *et al.*^{36–38}).

We parenthetically note that population-based designs (as opposed to family-based studies that avoid this conundrum) ought to be accompanied (as was commendably performed in the Willis-Owen *et al.*²⁷ study) by tests of population stratification,^{36–39} conjectured to be an important source of type II errors.⁴⁰ Regrettably, there appears to be a growing acceptance by journals for population-based studies without insisting on these precautions. This back sliding appears to be strongest in populations that are implied (without much real evidence) to be more ethnically homogenous than for example North American populations, such as Germany,^{41–43} Japan^{44–46} and China.^{47,48} The reader is referred to an informative article regarding the genetic structure of a Sardinian isolate⁴⁹ which shows how subtle and multifaceted is the concept of genetic homogeneity in human populations even those within a confined local geographical area.

A challenge in evaluating the Willis-Owen *et al.* study²⁷ is their use of the EPQ-N scale. A search of Medline revealed few if any studies that used this personality inventory to test association between EPQ-N and the 5-HTTLPR polymorphism, suggesting the possibility that the negative results reported by Willis-Owen *et al.* cannot be generalized and their conclusions are only germane to the EPQ-N. This question is especially relevant since the Sen *et al.*³² meta-analysis pointed to differences in personality inventory employed as an important source of inter-study heterogeneity.

Allelic heterogeneity

In comparison to the highly polymorphic *DRD4* gene, the serotonin transporter has a more conserved genotype. 5-HTTLPR is a variable number tandem repeat (VNTR) polymorphism consisting of 14–16 copies of 22 bp imperfect repeat sequences, also known as 44 bp Ins/Del because the most common polymorphisms are 16 repeats (long) and 14 repeats (short).^{10,50} The short allele showed lower expression in a dominant manner. Presence of one or two copies of the short allele significantly reduced the rate of transporter transcription, which was about 65% lower in brain and about 35% lower in lymphoblasts as compared with the respective regions of long/long homozygotes. Most studies of personality genetics have only genotyped 5-HTTLPR. An intron 2 VNTR (17 bp repeat), however, is also of interest.⁵¹ Linkage disequilibrium (LD) between the two loci (5-HTTLPR and intron 2 VNTR) was found in most of the studied

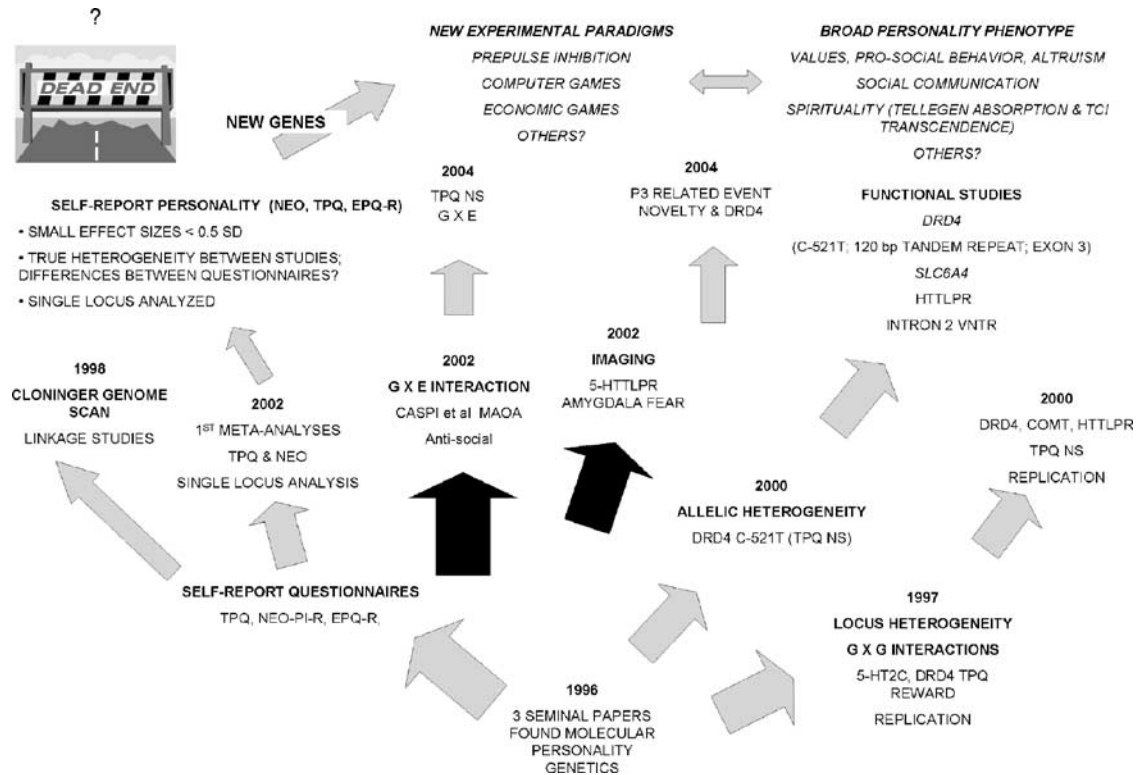


Figure 1 The evolution of molecular personality genetic research. The cartoon outlines what we consider some of the more important developments in personality genetics since its exciting beginnings in 1996. One research direction on the extreme left of the cartoon is the sole use of self-report questionnaires. Meta-analyses showed small effect sizes and true heterogeneity between studies for both the *DRD4* and *SLC6A4* genes and we conjecture that this is as good as it gets. Association studies based solely on self-report questionnaires are unlikely to explain more than a small fraction of the genetic variance in personality traits and are perhaps an evolutionary dead end in this field? Although such studies will continue to be important for generating putative candidates, by themselves the self-report design is unlikely to reveal the overall genetic architecture of personality or even offer convincing evidence for contribution of individual genes. However, self-report questionnaires will remain a useful first screen for provisional identification of candidates worthy of further investigation. Allelic and locus heterogeneity adds another order of complexity to genetic studies of personality, suggesting that large sample sizes and cutting edge haplotype analysis should be key elements in future studies. Functional studies of *DRD4* alleles revealed at least three sites of control (C-521T promoter, 120bp tandem repeat and exon III repeat) and surely *all* regions with functional significance need to be genotyped in future studies. We identify two breakthroughs in personality genetics viz. imaging genomics and gene \times environmental interactions. These new experimental strategies have far-reaching implications for the future of human behavioral genetics. These designs seem to be more robust than self-report questionnaires. Moreover, imaging genomics suggests that other strategies based on more direct measurement of brain activity (closer to the biological substrate of personality) including evoked potentials and other neurophysiological paradigms hold great potential for the future of this field. Candidates showing positive signals generated in self-report designs deserve to be tested across broader phenotypes and using diverse experimental designs. Following this broad approach, we expect that slowly, a body of evidence will accumulate showing a wide impact of common brain-expressed polymorphisms on somewhat discrete but related behaviors. Finally, a clearer understanding of how these genes influence behavior will eventually emerge. At the end of the day we, however, may have to accept a less than quantitative measure of validation than that provided by strict meta-analysis standards. Instead, a somewhat qualitative evaluation of the impact of genes on human behavior may well become the measure of gene effects. Finally, the evolutionary history of common polymorphisms and the use of animal models will continue to be important elements in the understanding of how genes affect human behavior.

populations: it ranged from moderate (e.g., in Europeans) to very strong (e.g., in Native Americans), while completely absent in some others (e.g., Chinese;⁵²). Allele-dependent differential enhancer activity of the polymorphic region in the second intron was demonstrated as different levels of reporter gene expression in embryonic stem cells⁵³ and in mouse embryo.⁵⁴ A thorough study by

Hranilovic and his co-workers⁵⁵ showed separate and combined effects of the intron 2 VNTR and 5-HTTLPR polymorphisms on the rate of transporter mRNA transcription in lymphoblasts. As discussed below, we have recently examined both *SLC6A4* polymorphisms in a study of smoking behavior and personality traits⁵⁶ as well as in a molecular genetic study of a musical phenotype.⁵⁷

Interestingly, a single-nucleotide variant (A to G) was detected in the sixth motif, present only in long variant of 5-HTTLPR, creating an AP2-binding site.^{58,59} In European American and African American populations, this polymorphism has a low frequency but the two polymorphisms are perhaps polymorphic enough if the size of the sample is large enough to provide reasonable statistical power. The long 'G' and long 'A' alleles are functionally distinct, in fact only the long A is associated with high levels of transporter mRNA expression. The function of the long variant when the G nucleotide is present is more similar to the 5-HTTLPR short allele, with a low level of mRNA. Carriers of the combination of long A and intron 2 VNTR 12 repeat alleles were at risk for suicide attempt,⁵⁸ consistent with a role for the purported role of this gene in depression, anxiety-related personality traits and similar phenotypes.

Other variations in the transporter gene, such as alternative splicing in 5' untranslated region,⁶⁰ multiple polyadenylation signals⁶¹ or SNP in 3'-untranslated region⁶¹ are also yet to be examined regarding personality genetics

Extreme phenotypes: do they help in validating associations?

A complimentary strategy in unraveling the complexities of personality genetics is the examination of subjects with extreme personality phenotypes and testing association between candidate genes in these groups.

For example, we genotyped a group of fibromyalgia patients⁶² for the 5-HTTLPR polymorphism prompted by the observation that these patients present with extreme scores on anxiety-related personality traits. As we expected, a highly significant excess of the short/short genotype was observed between patients and controls as well as when both ethnic groups were examined separately. Multivariate analysis (personality \times diagnosis \times polymorphism \times ethnicity) revealed significant main effects and ethnicity. The effect of 5-HTTLPR genotype did not quite attain significance at the $P=0.05$ level. Tests of between-subjects effects showed a highly significant effect of diagnosis on three of the TPQ personality traits (Novelty Seeking, Harm Avoidance and Persistence). Overall, fibromyalgia patients scored high on Harm Avoidance, low on Novelty Seeking and high on Persistence compared to a control group. A main effect of the 5-HTTLPR genotype was also observed on TPQ Harm Avoidance, consistent with the short allele's reported association with anxiety-related traits. These results confirm a previous German study⁶³ and demonstrate the robustness of the association between fibromyalgia and the 5-HTTLPR polymorphism, now observed in two independent studies across three distinct ethnic groups.

We also examined smokers, subjects who have been repeatedly reported to present with extreme scores on personality traits (high on Novelty Seeking and often high on anxiety-related personality traits as well), and

observed a significant excess of the 5-HTTLPR long allele and the 12-repeat intron VNTR in current smokers, past smokers and ever smokers, compared to participants who had never smoked.⁵⁶ The results from the population design were confirmed in the family-based analysis. A weak association was observed between Novelty Seeking and the *SLC6A4* intron 2 VNTR polymorphism and between Reward and 5-HTTLPR. Smokers in our study, regardless of gender, scored significantly higher on Novelty Seeking and did not differ on other personality traits. However, mediation analysis failed to substantiate the hypothesis that Novelty Seeking mediated the effect of *SLC6A4* on smoking. Some allelic variants of *SLC6A4* appear to independently contribute to both Novelty Seeking and smoking.

Animal studies

Murphy *et al.*⁶⁴ have reviewed the usefulness of animal models in exploring the complexities of human behavioral phenotypes, with a special focus on their group's development of an *SLC6A4* knockout mouse. This bottom-up approach (animal gene \rightarrow human phenotype) suggests that a major behavioral phenotype of the serotonin transporter mutant mouse is characterized by increased anxiety and fearfulness, which is consistent with many of the human studies of this gene.

A study by Ansorge *et al.*⁶⁵ skillfully illustrate the value of animal studies in understanding how human behavioral genes act. Although much of the evidence discussed above appears to support the contention that reduced *SLC6A4* expression generated by the presence of the 5-HTTLPR short allele is associated with abnormal affective and anxiety-like symptoms in humans, the neurochemical mechanism of this effect remains obscure. Especially confounding is that while SSRIs are effective anxiolytic agents (by inhibiting the serotonin transporter), the short 5-HTTLPR promoter allele (equivalent to an *endogenous* SSRI) is purported to predispose to anxiety. Ansorge *et al.*⁶⁵ resolved this paradox in a well-designed developmental study. They inhibited transporter expression during a limited period in early mouse development with fluoxetine which led to abnormal emotional behaviors in adult mice. This effect mimicked the behavioral phenotype of mice genetically deficient in transporter expression, which points to a critical role of serotonin in the maturation of brain systems that modulate emotional function in the adult. These results additionally suggest a developmental mechanism to explain how the short 5-HTTLPR promoter allele increases vulnerability to anxiety-related disorders.

Imaging

Weinberger and his colleagues⁶⁶ have pioneered the use of functional neuroimaging in the analysis of genotype-phenotype relationships in healthy individuals and have coined the term 'imaging genomics' for this new field. Their studies have strengthened the

connection between the serotonin transporter promoter region polymorphism and anxiety-related personality traits by showing an increased amygdala activation in subjects presented with fearful faces possessing the short 5-HTTLPR allele.⁶⁷ Such exciting conclusions, arrived at without recourse to self-report questionnaires and by studying only 28 subjects (albeit cleverly screened in advance for the long and short versions of the transporter), is extraordinary!

Weinberger and his associates have now confirmed the finding of 5-HTTLPR short allele-driven amygdala hyper-reactivity in a large independent cohort of 92 healthy subjects⁶⁸ and also impacts cingulate–amygdala interactions.⁶⁹ Interestingly, these genotype effects on amygdala function are consistent with a dominant short allele effect and are equally prominent in men and women. However, neither 5-HTTLPR genotype nor amygdala reactivity, nor genotype-driven variability in this reactivity was reflected in Harm Avoidance scores underscoring the apparent need for large numbers of subjects when the pencil and paper self-report strategy is employed. Although the imaging studies from the Weinberger group appear to be robust, a note of caution is appropriate since to our knowledge these studies are yet to be replicated by other investigators. Such replications are eagerly awaited.

Conclusions: SLC6A4 and anxiety-related personality traits

Overall, use of self-report questionnaires from control groups and subjects exhibiting extreme phenotypes, imaging studies and animal models all point to a credible association between the serotonin transporter gene and anxiety-related personality traits. Nevertheless, the effect size of this gene is at best small (0.2) by Cohen's definition.⁷⁰ Interestingly, despite the gender effects (women score higher on NEO-PI-R Neuroticism and TPQ Harm Avoidance), there is little consistent evidence that the association between *SLC6A4* is stronger in either gender. It is also of some interest that none of the genome-wide scans for anxiety-related personality traits showed linkage to chromosome 17q near the *SLC6A4* location (see next section). As is often noted, association studies provide significantly greater statistical power than linkage studies likely explaining the failure to detect linkage to *SLC6A* in genome-wide scans for anxiety traits.

Linkage studies of anxiety-related personality traits

Several genome-wide scans of anxiety-related personality traits have been reported.^{71–75} The first scan was by Cloninger *et al.*⁷⁴ and significant linkage was observed between TPQ Harm Avoidance and a locus on chromosome 8p21–23 that explained a considerable fraction of the trait variance. There was also significant evidence of epistasis between the locus on 8p and others on chromosomes 18p, 20p and 21q, and oligogenic interactions explained most of the variance

in this personality trait. A second genome-wide scan by Fullerton *et al.*⁷⁵ that used an extremely concordant–discordant sibling design screened a large UK population for subjects at the phenotypic extreme of the EPQ-R Neuroticism scale. Linkage was observed on 1q, 4q, 7p, 12q and 13q. These five loci met or exceeded the 5% genome-wide significance threshold of $\text{lod} = 3.8$. Weaker evidence for linkage on 8p, and on 11q was reported, but this nevertheless is of considerable interest since 8p and 11q overlap with regions flagged in the Cloninger study. Our own investigations also find evidence for a Harm Avoidance locus on chromosome 8p^{76,77} although at some distance from the other two findings and it is unclear whether all three studies identify the same signal despite the observation that chance variation in the location of linkage estimates is substantial.⁷⁸ We genotyped 24 microsatellite markers in 377 families with one or more siblings. Using three methods, we observed significant results (*P*-values from 0.002 to 0.0004) for linkage to TPQ Harm Avoidance in this region. A peak multipoint LOD score of 2.76 was obtained with the MLB method. Although the peak position varied somewhat according to the method for three methods, it was located at approximately 60 cM. One highly significant marker in our study is of particular interest since it is proximate (<0.5 cM) of the core haplotype that in several recent studies show significant association with a hotspot for schizophrenia near neuroregulin 1 (*NRG1*).⁷⁹

We conjecture, based on our results indicating linkage of TPQ Harm Avoidance to this schizophrenia 'hotspot' region, that the risk for major psychosis at the *NRG1* locus may be mediated by a personality trait. Anxiety-related personality traits such as TPQ Harm Avoidance are indices of emotional liability that are conjectured to predispose to psychopathology. Indeed, we and others have suggested that personality traits are endophenotypes for mental illness^{80–82} and the linkage findings of a Harm Avoidance and a schizophrenia locus at 8p strengthens this notion.

The involvement of other chromosomal areas that contribute to personality domains related to anxiety-related personality traits was suggested by genome scans of phenotypes such as alcoholism, panic disorder and depression since subjects with these disorders score high on neuroticism-related personality traits. A partial genome scan by Smoller *et al.*⁸³ used regions identified by QTL-mapping of anxiety phenotypes in mice to guide a linkage analysis of a large multiplex pedigree segregating panic disorder/agoraphobia. They found evidence of linkage to a locus on chromosome 10q for the anxiety-proneness and for panic disorder/agoraphobia to a locus on chromosome 12q13. Modest evidence of linkage to a region of chromosome 1q was noted. The chromosome 1p region is of particular interest since this area has been flagged by at least four studies for phenotypes that are related to anxiety-related personality traits including panic disorder,⁸⁴ alcoholism⁸⁵ and

eating disorders.⁸⁶ Another chromosomal area of interest is 7p.^{85,87,88} Further evidence for a putative involvement of chromosome 1p in anxiety-related personality traits is the identification of a syntenic rat locus on chromosome 5 that influences rodent emotionality.⁸⁹

Dopamine D4 receptor

Allelic heterogeneity

Allelic heterogeneity in the *DRD4* gene is a source of complexity in analyzing the role of this gene in behavior. Many *DRD4* polymorphisms have been identified in the genomic (5' upstream), coding and intronic regions. Moreover, LD between these polymorphisms is surprisingly weak^{90,91} sometimes even between adjacent SNPs, underscoring the importance of testing all genomic loci for association towards extracting the maximum amount of genetic information. The importance of fully assessing allelic heterogeneity was illustrated by the study by Grady *et al.*⁹² that explored the unusual degree of variation within the exon III repeat and its role in contributing risk to ADHD.

A mononucleotide (G)*n* repeat has been observed in intron 1 of *DRD4*, with alleles representing from six to ten guanine nucleotides present at this site.⁹³ Mill *et al.*⁹⁴ examined the role of the (G)*n* repeat in ADHD and found no evidence of association as did a Dutch group.⁹⁵ To our knowledge, this polymorphism is yet to be examined directly in personality studies. A 12 bp duplication in the N-terminal extracellular region that borders the first putative transmembrane domain and encodes a sequence of four amino acids in the first exon has been described.⁹⁶ This sequence occurs as a twofold repeat in the more common variant and is represented only once in the rarer allele. This polymorphism was associated by an Italian group with delusional disorder.^{96–98}

The first evidence that *DRD4* promoter region polymorphisms contribute to personality was the report by a Japanese group⁴⁶ who showed that a C-521T promoter-region SNP is both functional and associated with Novelty Seeking. C/C homozygotes had higher TPQ Novelty Seeking scores. Additionally, a transient expression method revealed that the T variant of the C-521T polymorphism reduces transcriptional efficiency. Several other studies have confirmed this association^{99–102} with one exception.¹⁰³ In African Americans, a significant three-way interaction (gender, C-616G genotype and C-521T genotype) was observed for NEO Extraversion.¹⁰¹

A second functional polymorphism in the *DRD4* promoter region is a 120 base-pair tandem duplication first identified by Seaman *et al.*¹⁰⁴ located 1.2 kb upstream of the initiation codon. The duplicated region contains consensus sequences of binding sites for several known transcription factors, suggesting that the long and short repeats may differ in their transcriptional activity. This polymorphism has been associated with attention deficit^{105–107} and also with

TPQ Novelty Seeking.¹⁰⁸ Subsequently, the longer allele (240 bp) was shown to display lower transcriptional activity than the short allele (120 bp)^{108,109} and homozygous subjects for the short allele scored higher on TPQ Novelty Seeking.¹⁰⁸

DRD4 exon III repeat region has functional consequences

Studies of G protein coupling,¹¹⁰ cyclic AMP synthesis,¹¹¹ *in vitro* expression¹¹² and chaperone-induced folding¹¹³ provide increasingly solid evidence that the shorter exon III repeats code for a more efficient gene at the level both of transcription, translation and second messenger generation compared to the D4.7 repeat.

DRD4 haplotypes

Three genomic regions have now been shown with various degrees of certainty to participate in the regulation of *DRD4* receptor synthesis: the promoter 120 bp tandem duplication,¹⁰⁹ the C-521T promoter SNP⁴⁶ and the exon III VNTR.^{110–113} One avenue of future research would be to examine all three loci in a single haplotype for their joint effect on expression. It would be of considerable value to know whether these various polymorphisms additively contribute to expression or is one locus a major determinant in regulating protein receptor levels? Similarly, it would be worthwhile when undertaking new studies to test at least these three *DRD4* loci for association with personality traits, especially in the absence of strong LD between these loci.

Of note is the latest investigation by Gervai *et al.*¹¹⁴ who examined a two-locus haplotype consisting of the exon III repeat and the C-521T promoter polymorphism in family trios studied for disorganized attachment (see Lakatos *et al.*^{115–117} for their earlier work and a Dutch study¹¹⁸ that reported a failure to replicate the association between attachment and *DRD4*), an early behavioral measure related to temperament. These authors showed that the transmission bias in the larger secure attachment group of infants was because of the low-rate transmission of the C-521T 'T':exon 3 seven repeat haplotype, suggesting that not carrying this haplotype may act as a resilience factor in the optimal development of early attachment. Interestingly, both the C-521T 'T' allele and the D4.7 repeat predict reduced *DRD4* receptor protein concentrations because of reduced translation.

In a German study,¹⁰⁰ carriers of the single 120 bp tandem repeat scored higher on Extraversion whereas carriers of the C-521T 'T' allele scored lower on this scale. Together, when gender, age and the haplotype were included in the analysis a considerable fraction of the variance in Extraversion was explained.

Extreme phenotypes

Downey *et al.*^{119,120} reported a decade ago that adult ADHD subjects score higher on TPQ Novelty Seeking especially if they smoke. It is therefore attractive to

assign the robust association between the D4.7 allele and ADHD¹²¹ to mediation by the personality trait of Novelty Seeking. Although a German study observed association between the D4.7 allele and TPQ Novelty Seeking scores in high-risk group of male and female 15-year adolescents, this association could not, however, be explained by the presence of either an ADHD or a *DRD4* by ADHD interaction. Similarly, in a recent study of parents from multiply affected ADHD families, association with a lifetime history of ADHD was shown with both Novelty Seeking and the D4.7 repeat,¹²² but the association between Novelty Seeking and ADHD did not appear to be because of variation in the *DRD4* D4.7 allele.

We have examined TPQ Novelty Seeking and the *DRD4* genotype in a group of women patients diagnosed with Fibromyalgia and expectedly found that these women score low on TPQ Novelty Seeking and notably show an under representation of the D4.7 allele.¹²³ Moreover, only within the Fibromyalgia group of women was an association observed between TPQ Novelty Seeking and D4.7 allele illustrating how worthwhile examining extreme phenotypes can be.

A German study¹²⁴ found that *DRD4* was associated with smoking status and Novelty Seeking in males but not in female subjects (who also scored higher on Novelty Seeking). Multiple regression analyses revealed that Novelty Seeking indeed mediated the relationship between *DRD4* and smoking in males.

Gene–Environment interactions

An important event of considerable impact in human behavioral genetics were publications by Caspi and his co-workers showing what was widely hypothesized but rarely demonstrated, that is, that both Nature and Nurture (Gene \times Environment interactions) jointly contribute to the determination of behavioral phenotypes.^{125–127} Remarkably, similar studies in non-human primates also show an interaction between the serotonin transporter polymorphism, depression/anxiety and alcoholism.^{128–130}

Finnish investigators have exploited the availability of early environmental information in their cohort study to test G \times E interactions for *DRD4* and TPQ Novelty Seeking¹³¹ in an enriched genetic model. Curiously, in this population, the D4.2 and D4.5 alleles were significantly more common in high scorers on Novelty Seeking¹³² (the reason for this is unclear but see Ekelund *et al.*¹³² for a discussion of possible explanations). When the childhood-rearing environment was more hostile (emotionally distant, low tolerance of the child's normal activity and strict discipline), the participants carrying D4.2 or D4.5 had a significantly greater risk of exhibiting high Novelty Seeking scores as adults. Similarly when the father, but not the mother, reporting more frequent alcohol consumption or drunkenness, there was an association between D4.2 and D4.5 and extreme Novelty Seeking scores.¹³³ These exciting results regarding personality traits and the impact of early environment eagerly await replication. Replication studies of the

effects of early environment on personality traits are keenly awaited.

An animal study strengthens the hypothesized role of early environment and its interaction with genotype in contributing to Novelty Seeking behavior. Two rat lines, with low emotionality/high Novelty Seeking versus high emotionality/low Novelty Seeking, were examined for the impact of enriched environment on adult temperament.¹³⁴ Raising rats in the enriched environment resulted in increased Novelty Seeking behavior, ethanol and saccharine consumption in adults from both rat lines. Why an enriched environment predisposes to these behaviors remains to be explained.

Linkage studies of personality traits

Several genome scans for substance abuse^{135–137} highlight a region on chromosome 11p that includes the *DRD4* locus. It is tempting to speculate that the signal for substance abuse in this region is due to the *DRD4* gene. *DRD4* as originally suggested³ contributes to a Novelty Seeking and impulsivity, personality type associated in some but not all studies with substance abuse.^{138,139}

Animal studies

Promoted by the first human studies suggesting an association between Novelty Seeking and *DRD4*, a mouse knockout model of the *DRD4* receptor was employed to explore a potential role for this gene in behavioral responses to novelty.¹⁴⁰ *DRD4* knockout mice exhibit reductions in behavioral responses to new environments. Moreover, the *DRD4* knockout mouse has also been shown to be supersensitive to alcohol and cocaine¹⁴¹ consistent with some human studies of this gene.

Four studies from Japan have examined *DRD4* polymorphisms and canine behavior.^{142–145} Twenty-three dog breed were studied for aggression, and association was observed between this trait and the exon III polymorphism.¹⁴²

In the genus *Equus* (horses), the *DRD4* exon III region includes an 18-bp repeat unit and there are inter- and intra-species differences in the number of repetitions. Because horses are unique among livestock species in the importance of temperament, Momozowa *et al.*¹⁴⁶ investigated the possible role of *DRD4* exon III on equine temperament in thoroughbred horses. They determined the sequences of this polymorphic region and administered a questionnaire survey to horse caretakers with questions about 20 different traits of their horses' temperament. Although there was no difference in the number of repeats among the 136 thoroughbred horses studied, two SNPs, one of which might cause an amino-acid change (A/G substitution; asparagine to aspartic), existed. Horses without the A allele had significantly higher Curiosity and lower Vigilance scores than those with the A allele at the A/G substitution.

Both for dogs and horses (and why not people?), temperament has been an important selective (by

human breeders for horses and dogs and by natural selection in people) character in breeding for both species and it seems likely that one of the genes contributing to differences in temperament is the *DRD4* receptor. Together, these findings suggest an attractive hypothesis that diversity in the sequence of the *DRD4* gene might partially influence differences in Novelty Seeking across mammalian species, including humans, horses, dogs and mice.

Evolutionary considerations

An intriguing feature of the *DRD4* exon III polymorphism is its recent evolutionary history revealed by the investigations of Kidd and his co-workers.^{147,148} It was estimated that the D4.7 allele arose prior to the upper Paleolithic era (~40 000–50 000 years ago). Further, the pattern of recombination at these polymorphic sites is the pattern expected for selection acting at the D4.7 VNTR itself. Kidd and his co-workers hypothesize¹⁴⁷ that the seven repeat increased in frequency (starting ~40 000–50 000 years ago) and is maintained as a balanced polymorphism.¹⁴⁹ It can only be speculated as to the behavioral phenotype that led to selection of the D4.7 allele and its maintenance as a balanced polymorphism. Following Bouchard and Loehlin,¹⁵⁰ Kidd and his co-workers suggest that a resource-depleted, time-critical, or rapidly changing environments might select for individuals with ‘response ready’ adaptations, whereas resource-rich, time-optimal or little-changing environments might select against such adaptations. These investigators suggest the notion that such a ‘response ready’ adaptation could have contributed to the out-of-Africa exodus and that allele frequencies of genes associated with such behaviors such as the D4.7 been positively selected for. This concept of ‘response ready’ personality type derives from the involvement of the D4.7 in ADHD, a problematic phenotype in an age when sitting attentively in the classroom is a requirement for academic achievement and success in a high tech society. Perhaps in the Upper Paleolithic period, the ‘response ready’ personality coded for in part by D4.7 was of some advantage whereas in the age of Googol and Microsoft it is decidedly not.

A second more general phenotype that we suggest is also determined for in part by the *DRD4* gene is altruism.⁹¹ We have recently presented some evidence that the balanced maintenance of both the D4.4 and D4.7 repeats in human evolution is possibly related to the need for diverse behavioral phenotypes in human populations partially determined by this gene, altruistic and prosocial (D4.4) vs a more aggressive, Novelty Seeking or perhaps even antisocial type (D4.7).

As we have discussed above, the D4.7 allele makes for a less efficient receptor and thereby reduces dopaminergic tone. We speculate that selective pressure and the maintenance of balanced polymorphisms across the *DRD4* gene (exon III, 120 bp tandem promoter repeat and C-521T SNP) allows ‘fine tuning’ of dopaminergic function that in higher

primates becomes critical for the maintenance of subtle but crucially adaptive differences in reward-directed behavior, aspects of cognition including attention (‘response ready’) and social communication.

Conclusions: DRD4 and Novelty Seeking

We deduce with some measure of certainty that *DRD4* indeed contributes to personality and behavioral traits related to a Novelty Seeking phenotype based on a broad view of the evidence including (1) studies with subjects exhibiting extreme phenotypes such as substance abuse, Fibromyalgia and ADHD; (2) animal models including knockouts; (3) G × E investigations from Finland and (4) the evolutionary history of the *DRD4* exon III polymorphism. Similar to common polymorphisms contributing to other complex phenotypes, the effect size of this gene is small and too few studies have been carried out that include all the haplotype information potentially available for this highly heterogeneous gene. As observed with the *SLC6A4* gene, there is little evidence that the association between Novelty Seeking traits is stronger in either male or female subjects.

Locus heterogeneity, gene × gene interactions and epistasis

How many genes are estimated to contribute to complex behavioral phenotypes including personality? A discussion of this question using rodent genetics as a background are found in the studies by Flint and his co-workers.^{151–153} For the pessimists among us it is notable that although over the past 15 years, more than 2000 quantitative trait loci (QTLs) have been identified in crosses between inbred strains of mice and rats, less than 1% have been characterized at a molecular level.¹⁵³ Even more sobering is that even if no more QTLs are mapped in rodent studies, at the present rate of progress (20 genes identified in 15 years) it will take 1500 years to find all the genes that underlie known QTLs. Flint is nevertheless optimistic and notes that new analytical tools, including probabilistic ancestral haplotype reconstruction in outbred mice, Yin-Yang crosses and in silico analysis of sequence variants in many inbred strains could make QTL cloning tractable. Flint notes that further high-resolution information at other QTLs might drive the estimate of average effect size below 5%. Altogether, finding genes for behavioral QTLs even in mice is no easy task and suggests that the road ahead in human personality genetics is likely to be long and undoubtedly frustrating on occasion.

Under some circumstances fewer genes than expected appear to contribute to temperament traits in rodent studies as shown by QTL analysis of the open field paradigm. The open field test is a rodent behavioral paradigm perhaps analogous to human Novelty Seeking. The QTL analysis indicates that the bulk of the phenotypic variance is due to ‘only’ six loci.¹⁵¹

Caspi *et al.*¹²⁷ have suggested that incorporating environmental information in human behavioral genetic models might result in far fewer genes contributing to these traits than expected but such genes, including crucial environmental information, are predicted to display larger effect sizes. This notion remains to be demonstrated but deserves serious consideration. A good bet is that the use of a robust phenotype definition such as an imaging paradigm (such as fear-generated amygdala response⁶⁸) coupled with early and reliable environmental information and more informative genotyping (accomplished by haplotype analysis across the genomic region), and epistatic interactions at different genetic loci might account for a large fraction of the variance of individual differences in anxiety-related personality traits.

Until recently it was assumed that alleles at separate QTLs contribute to most behavioral phenotypes additively. Recently, interest has shifted to the role of non-additive or epistatic interactions in contributing to complex phenotypes.¹⁵⁴ For example, there is widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's Personality Dimensions.¹⁵⁵ In its broadest sense, epistasis implies that the effect of a particular genotype on the phenotype depends on the genetic background. In its simplest form, this refers to an interaction between a pair of loci, in which the phenotypic effect of one locus depends on the genotype at the second locus. In the case of QTLs, epistasis describes the general situation in which the phenotype of a given genotype cannot be predicted by the sum of its component single-locus effects

HTR2C × *DRD4*

What is the evidence for specific gene × gene interactions including epistasis in personality studies? We first examined this topic in 1997¹⁵⁶ and observed that when present in the same individual, the *HTR2C* and *DRD4* polymorphisms account for 30% of the observed variance for Persistence and 13% of the variance for Reward-dependence scores. However, the number of subjects with both less common *D4DR* and *HTR2C* polymorphisms is small, underscoring the importance of verifying this interaction in a larger cohort. Our reported results were confirmed independently in a German study.¹⁵⁷

DRD4 × *COMT* × 5-HTTLPR

In a second study, we examined the interaction of three genes *DRD4*, 5-HTTLPR and *COMT* with TPQ Novelty Seeking.¹⁵⁸ In the absence of the short 5-HTTLPR allele and in the presence of the high enzyme activity *COMT* val/val genotype, Novelty Seeking scores are higher in the presence of the *DRD4* D4.7 allele. The effect of these three polymorphisms on Novelty Seeking was verified both by population- and family-based design. Again, this study was replicated in an independent German investigation.¹⁵⁹

DRD4 × *SLC6A4*: temperament in infants

Several independent studies have shown an interaction between the *DRD4* and *SLC6A4* genes in contributing to related phenotypes measured in infants and young children.^{117,160–165} As we first noted,^{164,165} the study of temperament traits in children offers the opportunity to study gene effects at a time in development when environmental effects are conjectured to be minimal and genetic associations might be more robustly demonstrated.

SLC6A4 × *GABA(A)*

Sen *et al.*¹⁶⁶ examined the *SLC6A4* 5-HTTLPR and a GABA (A) polymorphism (Pro385Ser) on Neuroticism and notably found evidence for an interaction between these two genes. 5-HTTLPR was strongly associated with Neuroticism, whereas in the presence of the alternate Pro/Ser genotype, 5-HTTLPR showed no association with this personality trait.

HTR2A × *COMT* and altered states of consciousness

A report by Ott *et al.*¹⁶⁷ examined the molecular genetic basis for individual differences in Tellegen's Absorption Scale or TAS,¹⁶⁸ an interesting phenotype not previously examined using a molecular genetic approach. Absorption represents a disposition to experience altered states of consciousness characterized by intensively focused attention. It is correlated with hypnotic susceptibility and includes phenomena ranging from vivid perceptions and imaginations to mystical experiences. Based on the assumption that drug-induced and naturally occurring mystical experiences share common neural mechanisms, it was hypothesized that Absorption is influenced by the T102C polymorphism affecting the 5-HT2a (*HTR2A*) receptor, which is known to be an important target for hallucinogens like LSD. Based on the pivotal role ascribed to the prefrontal executive control network for absorbed attention and positive symptoms in schizophrenia, it was further hypothesized that Absorption is associated with the *COMT* val158met polymorphism affecting the dopaminergic neurotransmitter system. (Interestingly, we have observed association between hypnotizability and the *COMT* gene^{169,170}.) In the Ott *et al.* study,¹⁶⁷ the group with the T/T genotype of the *HTR2A* T102C polymorphism had significantly higher Absorption scores while no main effect was found for the *COMT* polymorphism. However, the interaction between T102C and *COMT* genotypes was significant underlining the known functional interaction between the serotonergic and dopaminergic system. These findings are the first that point to biological foundations of Absorption.

5-HTTLPR × *AVPR1a*

We recently confirmed association between another serotonergic gene and TAS scores in a study of a musical phenotype, creative dance.⁵⁷ Association was observed between TAS scores and the arginine vasopressin 1a receptor *AVPR1a* (promoter-region repeats RS1 and RS3), *SLC6A4* haplotypes

(5-HTTLPR and intron 2 VNTR) and *AVPR1a* conditional on *SCL6A4*. (We have found the UNPHASED package a useful program that allows testing of gene by gene interactions^{171,172}.) A highly significant interaction was also observed between *AVPR1a* and *SCL6A4* intron 2 VNTR and TPQ Reward. The association between *AVPR1a* and TPQ Reward is of interest since this personality dimension taps into elements of empathy, a key element in social behavior and communication. Interestingly, *AVPR1a* was associated with autism^{173–175} whose core deficits are in the domain of social cognition. The *AVPR1a* promoter region repeat regions are of particular interest since in non-primates this gene has a profound effect on social behaviors and social communication,^{176–177} phenotypes that deserve to be more studied at the molecular genetic level in humans. Only a few investigations have so far examined this gene in humans but notably several reports now link *AVPR1a* to aspects of human social communication.^{57,173–175,178,179}

Other genes

Table 1 presents information regarding other genes that have been investigated for association with personality traits. Quick perusal of the Table reveals the gap in number of independent investigations between all other genes so far studied and *DRD4* and *SLC6A4* and explains why in the current review we have mainly focused on these two genes.

Beyond self-report temperament measures

Traits such as altruism,⁹¹ spirituality,¹⁶⁷ social communication,^{57,179} empathy and shyness¹⁸⁰ to name just a few novel 'personality' phenotypes are likely to be studied in greater depth in the future. Moreover, some of these phenotypes might best be studied by laboratory-based paradigms. Restricting conclusions to evidence derived from meta-analyses that are based on self-report questionnaires is suggested to be too conservative a strategy and it might be time to change the game plan and look at the forest and not only the trees. GeneCard (<http://www.genecards.org/index.shtml>) lists 23 OMIM phenotypes associated with the *DRD4* gene and 44 phenotypes associated with the *SLC6A4* gene. Evaluating the role of these two genes towards a broad understanding of human personality surely needs to consider all the available evidence based on all these phenotypes.

We suggest that some novel experimental paradigms such as evoked potentials,^{181,182} prepulse inhibition¹⁸³ and some computer game models¹⁸⁴ may also prove useful in unraveling the role of specific genes in contributing to the multifaceted dimensions of human personality. Knowledge of a gene's action at a lower level of brain organization such as those mediated by prepulse inhibition^{185–187} and evoked potentials^{188,189} may well clarify the role of particular polymorphisms in higher order behaviors such as personality constructs.

A limiting factor in the study of the *DRD4* receptor and its role in temperament traits is the lack of specific radiotracers and the lack of imaging studies regarding *DRD4*.¹⁹⁰ However, progress has been made in identifying brain regions involved in facets of Novelty Seeking. For example Passamonti *et al.*¹⁹¹ have identified brain areas involved in impulsivity and the role of a specific polymorphism in their activation. They studied the relationship between MAO A genotypes and brain activity elicited by a response inhibition task (Go/NoGo task) using BOLD fMRI. A greater BOLD response in the right ventrolateral prefrontal cortex was observed in high-activity allele carriers, whereas a greater response in the right superior parietal cortex and bilateral extrastriate cortex was observed in low-activity allele carriers.

A report by Sobel *et al.*¹⁸⁹ hypothesized that *DRD4* is involved in the modulation of the cortical response to novelty as reflected by the auditory evoked novelty P3 event-related potential. These authors observed an interactive effect of *DRD4* exon III genotype and the eye-blink rate, a measure of central dopaminergic activity, on the novelty P3. These findings suggest that the *DRD4* exon III polymorphism influences the processing of novelty and that this influence depends on tonic dopaminergic activity. These conclusions are notable since they lend support to the original findings that *DRD4* mediates NS behavior^{3,4} but demonstrate the association using a unique paradigm in a relatively small number of subjects.

A good example of the bottom-up approach strategy in elucidating human behavioral traits is the current flurry of interest in the SNAP 25 gene especially regarding ADHD. SNAP-25 is an integral component of the vesicle docking and fusion machinery mediating regulated release of neurotransmitters. The SNAP-25 gene is within the deletion region in the *coloboma* mice mutant strain hemizygous for an approximately 2-cM deletion of mouse chromosome 2.¹⁹² These mice are characterized by several features most notably marked hyperactivity that begins between postnatal days 11 and 14.¹⁹³ Barr *et al.*¹⁹⁴ were the first to report an association between this gene and human ADHD, a beautiful example of bottom-up thinking and experimentation.

Evolutionary considerations are also important in understanding the role of some genes in behavior. For example, investigations of ASPM (abnormal spindle-like microcephaly associated) across animal phyla indicate a role for ASPM in brain size (so-called 'IQ' domains) as well as suggesting a role for this gene in human cognition.¹⁹⁵ Similarly, the putative role of FOXP2 in human speech is better understood in light of the molecular evolution of this gene.^{196–198}

Faced with the multiple challenge posed by small effect sizes, polygenic inheritance, environmental influences and the limitations of self-report questionnaires, it seems unlikely that future studies based solely on a single instrument or experimental paradigm will substantially improve our understanding of how genes such as *DRD4* and *SLC6A4* impact on

Table 1 Other genes associated with personality

<i>Gene</i>	<i>Polymorphism</i>	<i>Trait</i>	<i>Comments</i>	<i>Reference</i>
DRD4	Null mutation 1st exon; 21 bp deletion (codons 36–42)	OCD, panic disorder	The mutation was identified in a single individual suffering from obsessive-compulsive disorder and panic disorder	Cichon <i>et al.</i> ¹⁹⁹
DRD2	TaqA1 +	Neuroticism anxiety	However, for men observed a specific association between low neuroticism-anxiety and the A1 + allele	Wacker <i>et al.</i> ²⁰⁰
DRD2	P3 ERP Oddball task	Zuckerman's Sensation Seeking	A small P3 amplitude, high sensation-seeking, and the presence of the A1 allele associated with alcoholism risk	Ratsma <i>et al.</i> ²⁰¹
DRD2	Imaging fMRI PET	TPQ NS	Negative correlation between novelty seeking and DRD2 availability bilaterally in the insular cortex	Kaasinen <i>et al.</i> ^{202,203}
DRD2	Imaging SPECT IBZM	Neuroticism	Striatal DRD2 densities correlated with neuroticism scores	Lee <i>et al.</i> ²⁰⁴
DRD2 DRD4	Minor DRD2 alleles	TPQ NS	Combined DRD2 and DRD4 polymorphisms contribute more markedly to NS	Noble <i>et al.</i> ²⁰⁵
DRD3	<i>Ball</i>	Alcoholism	No association with alcoholism	Gorwood <i>et al.</i> ²⁰⁶ and Limosin <i>et al.</i> ²⁰⁷
SLC6A4	Missense mutation	OCD	Uncommon coding region SLC6A4 mutation, Ile425Val, in two unrelated families with OCD and other serotonin-related disorders; an example of Risch's 'low hanging fruit'?	Ozaki <i>et al.</i> ²⁰⁸
5-HT2A 5-HT6	A-1438G C267T	TCI	5-HT2A A-1438G with self-determinism and self-transcendence 5-HT(6) C267T and self-transcendence.	Ham <i>et al.</i> ²⁰⁹
5-HT2A	A-1438G	NEO-PI-R	A/A of -1438G/A (or T/T of 102T/C) lower in Neuroticism and higher in Conscientiousness	Tochigi <i>et al.</i> ²¹⁰
5-HT3A	C178T	TPQ HA	Associated with Harm Avoidance in women.	Melke <i>et al.</i> ²¹¹
5-HT1A	C-1016G	NEO N TPQ HA	Neuroticism with G allele showing higher scores than individuals homozygous for the C variant on both scales	Strobel <i>et al.</i> ⁴³
MAO A	Promoter repeat (short)	Cluster B DSM IV	26.0% of cluster B patients were hemi- or homozygous for the low-activity variant of the MAOA genotype, compared to 16.4% in the control group	Jacob ²¹²
MAO A	Promoter repeat	TPQ HA-evoked potential	Homozygosity for the four-repeat allele tendency for a higher total score on HA; no association with auditory-evoked potential	Yu <i>et al.</i> ^{213–214}
MAO A	Promoter repeat	Buss-Durkee	Low-activity three-repeat allele increased susceptibility to antisocial-violent behavior and aggressiveness	Gerra <i>et al.</i> ²¹⁵
NET	T-182C G1287A (silent poly-morphism)	TPQ Reward Methylphenidate Response ADHD	Associated with TCI Reward Positive association with methylphenidate	Ham <i>et al.</i> ²¹⁶ Yang <i>et al.</i> ²¹⁷
	G1287A (silent poly-morphism)	TPQ	No association	Samochowiec <i>et al.</i> ²¹⁸

Table 1 continued.

Gene	Polymorphism	Trait	Comments	Reference
Alpha(2c)-adrenoceptor	del322–325		No association	Tsai <i>et al.</i> ²¹⁹
β -1 Adrenergic receptor	Ser49Gly Arg389Gly	NEO extraversion	Presence of a Gly49 allele was associated with an increased odds of having low or very low extraversion	Tsai <i>et al.</i> ²¹⁹ Stein <i>et al.</i> ²²⁰
Histamine N-methyltransferase	Thr105Ile	TPQ HA alcoholism	Decreased levels of brain histamine consequent to the Thr105 allele may result in higher levels of anxiety and, as a consequence, vulnerability to alcoholism	Oroszi <i>et al.</i> ²²¹
AP-2	Intron CAAA REPEAT	KSP anxiety traits	Women being homozygous for the long AP-2b allele displayed lower scores for anxiety-related personality traits and indirect aggression than women with at least one short allele	Damberg ²²² and Damberg <i>et al.</i> ²²³
BDNF	Val66met	Anxiety-related personality traits	In some but not all studies, the met allele is associated with lower N scores	Willis-Owen <i>et al.</i> , ³³ Lang <i>et al.</i> , ²²⁴ Itoh <i>et al.</i> , ²²⁵ Tsai <i>et al.</i> , ^{226,229} Sen <i>et al.</i> , ²²⁷ Jiang <i>et al.</i> , ²²⁸

personality. The current state of affairs regarding questionnaire-based temperament studies may be as good as it gets, and it is not very good. We therefore urge a broader, multidisciplinary study of genes likely to contribute to a range of related phenotypes towards arriving at a comprehensive picture of how genes contribute to personality, defined by Webster as the quality or state of being a person or the complex of characteristics that distinguishes an individual.

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