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ABSTRACT

The dopamine receptor gene DRD3 and in particular the single nucleotide polymorphism Ser9Gly has been extensively investigated and found to have potential association with a wide variety of conditions. These include essential tremor, unipolar and bipolar depression, as well as a loose association with schizophrenia. Evaluation of 1) these known associations with DRD3, 2) the recent finding of Costas and colleagues that a haplotype containing Ser-9 is associated with protection from schizophrenia, and 3) an extant trait model of personality, leads to the hypothesis that an allele DRD3/Ser codes for trait aggression by Mendelian recessive inheritance. The implications of this hypothesis are that 1) DRD3 is a pleiotropic gene having allelic polymorphism related to both behavior and disease, and 2) models of personality based on genetic traits hold promise. In the area of schizophrenia, the hypothesis implies that schizophrenic patients can be divided into two broad classes: those having genotype DRD3/Ser/Ser and those who lack this homozygosity. The hypothesis of the association of DRD3 with trait aggression could be readily evaluated by testing groups of healthy individuals by personality inventory focused on aggression and by biochemical assay of neurotransmitter levels.

INTRODUCTION

The dopamine D3 receptor gene DRD3, in particular the single nucleotide polymorphism Ser9Gly, has been extensively investigated. The gene on chromosome 3 codes for a protein that responds to the neurotransmitter dopamine in order to trigger signals within the central nervous system. The D3 receptor function is one of inhibition: it inhibits the enzyme adenylyl cyclase, as well as dopamine-mediated secretion of renin. The DRD3 receptor has thus been implicated in salt retention and hypertension [1,2], as well as conditions like essential tremor [3,4], and both unipolar and bipolar depression [5,6].

The DRD3 receptor has long been studied as a locus possibly associated with schizophrenia, but the results have been inconclusive. In a meta-analysis by Shi and colleagues [7] done in 2008, the DRD3 gene was not among the top seven candidates for predisposition to schizophrenia. However, in 2009 Costas and colleagues [2] presented a study in which they found that a haplotype of DRD3 associated with the Ser9Gly polymorphism (Ser-9 allele) had a significant

protective effect from schizophrenia in three independent populations of European origin. They found that the frequency of the protective haplotype varied greatly worldwide, being very low in sub-Saharan Africa and highest in the Mideast. They concluded, by examining the patterns of linkage disequilibrium around the DRD3 gene, that the protective haplotype had reached high frequencies in non-African populations due to strong selection acting on a linked functional polymorphism, presumably the Ser variant of Ser9Gly. The authors commented that the selective evolutionary force acting on DRD3 was "totally unknown."

HYPOTHESIS

The known functions and associations of gene DRD3, and the finding by Costas *et al.* that the gene is related to protection from schizophrenia, leads to the following hypothesis:

A Ser-9 allele denoted by DRD3/Ser codes for trait aggression ("trait A") by Mendelian autosomal recessive inheritance. The Ser-9 variant is a necessary but not sufficient requisite for expression of trait A.

EVALUATION

The hypothesis that an allele DRD3/Ser codes for trait A by autosomal recessive inheritance comes from five areas:

1. *Mutation in a gene that codes for an inhibitor can lead to a new recessive trait.* Since DRD3 functions as an inhibitor, a recessive trait could appear if a mutation occurred and eventually attained the homozygous state. That is, gene function would need to be blocked on both homologous chromosomes, leading to a "release of inhibition" and the expression of the variant allele in a new recessive trait. In our case, DRD3/Gly is assumed to be dominant with respect to DRD3/Ser. When the homozygous genotype DRD3/Ser/Ser is attained, then trait A is expressed.

2. *An extant genetic model of personality predicts that aggression is a trait that can give protection from schizophrenia.* In a genetic model of personality [8] aggression appears as a phenotypic behavioral trait that occurs in healthy individuals. In populations where the prevalence of trait A is substantial, the trait appears as one that gives relative protection from schizophrenia. In the model, on the basis of archetypal family pedigrees, trait A was concluded to be autosomal recessive [8]. Since the study of Costas *et al.* [2] showed that a haplotype corresponding to DRD3/Ser conferred protection from schizophrenia, it follows that the literature should be examined for evidence that a) DRD3/Ser is related to trait aggression, and b) the mode of inheritance is recessive.

3. *Evidence that an allele DRD3/Ser is related to aggression is suggested by a published meta-analysis.* We refer now to the study done in 2003 by Munafò and colleagues [9], who examined associations between polymorphisms in "candidate genes" and personality factors in healthy adults. The authors collated the results of five separate studies of the relationship of DRD3 Ser9Gly polymorphism with aggression. The studies were done in Australia, France, Germany, Israel and the USA, and in all five studies it was the homozygous

DRD3/Ser/Ser genotype which had the highest frequency (Ser/Ser genotype frequency being in the narrow range of 45 to 53 percent). In the meta-analysis, the results were pooled and the two homozygote groups and the heterozygote group were tested against each other for difference in aggression. The difference in aggression between the Ser/Ser genotype when compared with the group of Gly/Gly individuals was the most significant ($p<0.05$). This result is some evidence for the association of DRD3/Ser with aggression and is not inconsistent with the Ser variant of the allele being recessive.

4. *Studies of unipolar and bipolar depression are consistent with an allele DRD3/Ser being related to aggression.* Unipolar depression has been found [5] to be associated with DRD3 genotypes Gly/Gly and Gly/Ser, i.e., with the phenotype(s) posited to be "low" in trait aggression. This is consistent with what is known about the personality of unipolar patients. Young and colleagues [10] indicated that unipolar patients tended to score high in "Harm Avoidance" but low in "Novelty Seeking," which is consistent with a personality type low in trait aggression. In bipolar disorder (which includes hypomanic patients), personality testing for aggression [11] reveals that bipolar I patients (with manic episodes) tend to score higher in aggression than bipolar II patients (no manic episodes). Significantly, in a study from Taiwan, Lee and colleagues [6] found that the Ser/Ser genotype of DRD3 characterized bipolar I patients. These results suggest that trait aggression is a personality factor that can aid in delineation of the various categories of depression and that the genotypes Gly/Gly and Gly/Ser correspond to "low" aggression, while the genotype Ser/Ser is the one that corresponds to "high" aggression.

5. *Studies of essential tremor (ET) are consistent with allele DRD3/Ser being related to aggression.* Essential tremor has also been found in some studies to have association with the DRD3 gene [3,4], the association being with the Gly/Gly and Gly/Ser genotypes, i.e., those posited to correspond to "low" aggression. Significantly, it has been found from personality testing that ET patients tend to have unaggressive personalities. Chatterjee and colleagues [12] in the USA found that patients with ET tended to score higher on the Harm Avoidance scale on the TPQ personality questionnaire, while Lorenz and colleagues [13] in a study from Germany found that ET patients had very low scores averaging in the 11th percentile of the Psychoticism scale of the Eysenck Personality Questionnaire, corresponding to "a more tender-minded personality type." Again, these studies of ET are consistent with the Gly/Gly and Gly/Ser genotypes corresponding to "low aggression" and Gly being the dominant (or incompletely dominant) allele.

DISCUSSION

Given that much attention has been given to DRD3 gene function for the past decades, the question arises why an association of DRD3 with aggression has not been found. There are several possible reasons:

First, the association has been reported in the literature – in the meta-analysis of Munafò *et al.* [9]. As noted above, the pooled data showed evidence for an association between DRD3 Ser9Gly and aggression with a level of

significance of $p<0.05$. However, Munafò *et al.* conducted a deeper statistical analysis of their results and concluded that just about all of their positive results – indeed for all the candidate gene polymorphisms tested – lost statistical significance when various corrections were made. Thus, the essence of the paper was one of "negative results," and evidently the paper was not widely perused.

Second, the term "aggression" has pejorative connotations. Aggression tends to be considered an aberrancy in human behavior, rather than a normal trait, and is not routinely tested in a quantitative manner. Specific questionnaires for the testing of trait aggression do exist (like the Brown-Goodwin Aggression Scale), but they are little used. The term "aggression" does not even appear in the index of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association), with patients having disorders of aggression usually being placed in the category of "Antisocial Personality Disorder." Aggression does not occur overtly in most theories of personality like the frequently used Five Factor Model [14]; instead it is dispersed in various broad categories like "Openness" and "Extraversion."

Third, the allele DRD3/Ser has become a common variant in most areas of the world [2] and its frequent appearance in both study and control groups may hide the effect that is being tested for. DRD3/Ser is posited to be a high frequency allele coding for a recessive trait, which is somewhat unusual. Finally, most studies report only the Ser9Gly aspect of DRD3, rather than the more relevant haplotype identified by Costas *et al.* [2].

TESTING THE HYPOTHESIS

The hypothesis of the association of DRD3 with trait aggression could be readily evaluated by the controlled testing of groups of healthy individuals by personality inventory focused on aggression and by assays of neurotransmitter-related levels. The mode of recessive inheritance could be tested for by DNA assay in family pedigrees.

POSSIBLE IMPLICATIONS

The implications of finding an association of gene DRD3 with aggression fall into several categories:

1. The role of neurotransmitters in the expression of aggression would be clarified. Other sites, such as MAO-A [15] and COMT [16], are likely to be involved, and epistatic interaction between the genes is likely to be complex.

2. DRD3 would be shown to be a pleiotropic gene with alleleic polymorphism related to both behavior and disease by various mechanisms of inheritance. The interaction of DRD3 with other diseases – in particular so-called "psychosomatic diseases" that have been traditionally associated with "low aggression," like rheumatoid arthritis – would need to be examined.

3. In the area of schizophrenia, the finding would imply that schizophrenic patients could be divided into two main categories: those who are homozygous for DRD3/Ser ("high or modulated aggression") and those who are not ("inhibited aggression"). It would clarify the result of Costas *et al.* [2] that DRD3/Ser gives protection from schizophrenia. The trait model referred to earlier [8] implies that

DRD3/Ser would not be “protective” in all populations, and furthermore, a second complementary gene (coding for “sanguinity” and yet to be discovered) could also be protective. The two genes are posited to be "entangled" in the sense that either trait aggression or sanguinity must be expressed in any healthy individual. This dichotomy could explain why a recent meta-analysis by Nunokawa *et al.* [17] failed to find evidence for a protective haplotype related to DRD3.

4. Verification of the hypothesis would imply that trait models of personality based on specific genes hold promise.

5. The finding would have application in evolutionary anthropology. Since DRD3/Gly is the ancestral allele present in other primates and DRD3/Ser is the variant [2], this could lead to a hypothesis that the last common ancestor of *Homo sapiens* and the great apes was “low” on trait aggression.

6. In the area of population genetics it would explain the query of Costas *et al.* [2] as to why the allele DRD3/Ser showed such rapid evolution after the “Out of Africa” ancestral migrations of modern man. Our hypothesis is that DRD3/Ser codes for a behavioral trait, namely aggression, which could logically offer individuals carrying the trait an immediate reproductive advantage. Finally, if the hypothesis is correct, the world map of the distribution of the haplotype associated with DRD3/Ser presented in the paper by Costas *et al.* [2], showing a nidus for expansion of the allele in the Mideast, would take on new meaning – as a current map of the worldwide distribution of trait aggression.

BIBLIOGRAPHY

1. Asico LD, Ladines C, Fuchs S, Accili D, Carey RM, Semeraro C, Pocchiari F, Felder RA, Eisner GM and Jose PA. Disruption of the dopamine D3 receptor gene produces renin-dependent hypertension. *Journal of Clinical Investigation* 1998;102(3):493-8.

2. Costas J, Carrera N, Domínguez E, Vilella E, Martorell L, Valero J, Gutiérrez-Zotes A, Labad A and Carracedo A. A common haplotype of DRD3 affected by recent positive selection is associated with protection from schizophrenia. *Human Genetics* 2009;124:607-13.

3. Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde J-P, Lucotte G and Sokoloff P. A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. *Proceedings National Academy Sciences USA* 2006;103:10753-8.

4. García-Martín E, Martínez C, Alonso-Navarro H, Benito-León J, Puertas I, Rubio L, López-Alburquerque L, Agúndez JAG and Jiménez-Jiménez FJ. Dopamine receptor D3 (DRD3) genotype and allelic variants and risk for essential tremor. *Movement Disorders* 2009;24:1910-15.

5. Dikeos DG. Association between the dopamine D3 receptor gene locus (DRD3) and unipolar affective disorder. *Psychiatric Genetics* 1999;9(4):189-95.

6. Lee S-Y, Chen S-L, Chen S-H, Huang S-Y, Tzeng N-S, Chang Y-H, Wang C-L, Lee IH, Yeh TL, Yang YK and Lu R-B. The COMT and DRD3 genes

interacted in bipolar I but not bipolar II disorder. *World Journal of Biological Psychiatry* 2011;12(5):385-91.

7. Shi J, Gershon ES and Liu C. Genetic associations with schizophrenia: Meta-analyses of 12 candidate genes. *Schizophrenia Research* 2008;104:96-107.

8. Benis AM. A theory of personality traits leads to a genetic model for borderline types and schizophrenia. *Speculations in Science and Technology* 1990;13:167-75.

9. Munafò MR, Clark TG, Moore LR, Payne E, Walton R and Flint J. Genetic polymorphisms and personality in healthy adults: A systematic review and meta-analysis. *Molecular Psychiatry* 2003;8:471-84.

10. Young LT, Bagby RM, Cooke RG, Parker JDA, Levitt AJ and Joffe RT. A comparison of Tridimensional Personality Questionnaire dimensions in bipolar disorder and unipolar depression. *Psychiatric Research* 1995;58:139-43.

11. Garno JL, Gunawardane N and Goldberg JF. Predictors of trait aggression in bipolar disorder. *Bipolar Disorders* 2008;10(2):285-92.

12. Chatterjee A, Jurewicz E, Applegate L and Louis E. Personality in essential tremor: further evidence of non-motor manifestations of the disease. *Journal of Neurological and Neurosurgical Psychiatry* 2004;75(7):958-61.

13. Lorenz D, Schwieger D, Moises H and Deuschl G. Quality of life and personality in essential tremor patients. *Movement Disorders* 2006;21(8):1114-8.

14. Digman JM. Personality structure: Emergence of the five-factor model. *Annual Review of Psychology* 1990;41:417-40.

15. Alia-Klein N, Goldstein RZ, Kriplani A, Logan J, Tomasi D, Williams B, Telang F, Shumay E, Biegon A, Craig IW, Henn F, Wang G-J, Volkow ND and Fowler JS. Brain monoamine oxidase A activity predicts trait aggression. *Journal of Neuroscience* 2008;28(19):5099-5104.

16. Volavka J, Bilder R and Nolan K. Catecholamines and aggression: The role of COMT and MAO polymorphisms. *Annals NY Academy of Sciences* 2004;1036: 393-8.

17. Nunokawa A, Watanabe Y, Kaneko N, Sugai T, Yazaki S, Arinami T, Ujike H, Inada T, Iwata N, Kunugi H, Sasaki T, Itokawa M, Ozaki N, Hashimoto R and Someya T. The dopamine D3 receptor (DRD3) gene and risk of schizophrenia: Case-control studies and an updated meta-analysis. *Schizophrenia Research* 2010;116:61-67.