Vulpe C, Levinson B, Whitney S, Packman S, Gitschier J (1993) Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. Nat Genet 3:7–13

Wakamatsu N, Kobayashi H, Miyatake T, Tsuji S (1992) A novel exon mutation in the human β-hexosaminidase β subunit gene affects 3′ splice site selection. J Biol Chem 267: 2406–2413

Address for correspondence and reprints: Nathalie Ronce, Unité de Génétique, Hôpital Bretonneau, 2 Boulevard Tonnellé, 37044 Tours Cédex, France. E-mail: ronce@med.univ-tours.fr

© 1997 by The American Society of Human Genetics. All rights reserved.

0002-9297/97/6101-0032$02.00

Am. J. Hum. Genet. 61:238-239, 1997

Nonreplication of Linkage Disequilibrium between the Dopamine D4 Receptor Locus and Tourette Syndrome

To the Editor:

Grice et al. (1996) recently reported linkage disequilibrium between the seven-repeat allele (DRD4*7R) of the exon 3 VNTR polymorphic site at the D4 dopamine receptor locus and expression of chronic multiple tics and Tourette syndrome (TS). The study cohort encompassed 64 family trios each of which consisted of an affected person and two parents, of whom at least one was heterozygous for the DRD4*7R. Fifty-two of the trios stemmed from four large TS kindreds; the remaining 12 were independent nuclear-family trios. Grice et al. pointed out that confirmation of their finding depends on either replication or the identification of a transmitted functional mutation.

In the present study we evaluated different genotypes at the D4 dopamine receptor locus of ≤102 TS index probands and their parents. Subgroups of the patients, encompassing children, adolescents, and young adults, have been described elsewhere (Hebebrand et al. 1993; Nöthen et al. 1994*a,* 1994*b*). By use of the transmission-disequilibrium test (TDT) (Spielman et al. 1993), the following polymorphisms at the DRD4 locus were investigated: (1) the DRD4*7 allele, against all other alleles at the multiallelic VNTR polymorphism in exon 3 (van Tol et al. 1992; Lichter et al. 1993), in 102 trios; (2) the 13-bp deletion in exon 1, with 2% frequency of the deletion allele in the German population (Nöthen et al. 1994*a*), in 102 trios; (3) the two-allele system in exon 1, encompassing an allele with a 12-bp duplication (Catalano et al. 1993), in 102 trios (we found an additional, third allele for the 12-bp duplication in exon 1, characterized by the threefold occurrence of the 12-bp unit); and (4) the two-allele system based on the arginine→glycine substitution at position 11 in exon 1, in 87 trios (Cichon et al. 1995). The variants tested in our study include all known variants of the DRD4 gene that alter the amino acid composition of the receptor and have a frequency of >1% in Caucasians. Genotypes were determined as described elsewhere (Lichter et al. 1993; Nöthen et al. 1994*a;* Cichon et al. 1995).

None of the two-sided TDTs for the investigated polymorphisms reached a P of <.05. Because of the attempt to replicate the findings of Grice et al.(1996), the transmission patterns of the DRD4*7R allele deserve special consideration. A total of 58 parents were heterozygous for the DRD4*7R allele. In these meioses the DRD4*7R allele was transmitted 32 times and was not transmitted 26 times. This reveals a P of .26, by use of the one-sided exact binomial TDT.

For power calculations, we took the findings of Grice et al. (1996) as given. These investigators had performed three TDTs based on inclusion and exclusion of inferred genotypes and two different diagnostic models in extended pedigrees; the range of transmitted DRD4*7R alleles from parents heterozygous for this allele was 68%–73%. On the basis of our 58 heterozygous parents, the exact randomized one-sided binomial TDT has 86%–98% power to detect transmission disequilibrium for a significance level of 5%.

The two-sided TDT for the Gly11Arg polymorphism had a P of .06 (not corrected for multiple testing) on the basis of the binomial test; only five parents were heterozygous, and in all five cases the wild-type allele (11Gly) was transmitted to the index proband.

The Gly11Arg variant is seemingly in linkage disequilibrium with the exon 3 VNTR polymorphism. The following haplotypes bearing the 11Arg allele were observed: 11Arg-DRD4*2R (n = 2), 11Arg-DRD4*6R (n = 1), and 11Arg-DRD4*7R (n = 2). None of the haplotypes contained the DRD4*4R allele, which is the most frequent (.69 of nontransmitted parental alleles) among the VNTR alleles. The probability of nonobservation of the haplotype 11Arg-DRD4*4R is low (.0033); however, on use of the two-sided TDT, the DRD4*4R allele in itself was not linked or associated with TS (P = .92). The two-sided TDT for the haplotype consisting of the DRD4*4R and the 11Gly alleles revealed a P of .68. In conclusion, although there seems to be linkage disequilibrium between Gly11Arg and the exon 3 VNTR polymorphism, no indication for transmission disequilibrium in TS was detected.

We conclude that in the families that we have studied there is no evidence that the DRD4*7R allele of the exon 3 VNTR is linked or associated with TS.

Thus, we were not able to replicate the findings of Grice et al. (1996).

JOHANNES HEBEBRAND, MARKUS M. NÖTHEN, ANDREAS ZIEGLER, BIRGIT KLUG, HELGE NEIDT, KATJA EGGERMANN, GERD LEHMKUHL, FRITZ POUSTKA, MARTIN H. SCHMIDT, PETER PROPPING, AND HELMUT REMSCHMIDT

Clinical Research Group
Department of Child and Adolescent Psychiatry
Philipp's University of Marburg
Marburg, Germany

Acknowledgment

This study was supported by the Deutsche Forschungsgemeinschaft.

References

Catalano M, Nobile M, Novelli E, Nöthen MM, Smeraldi E (1993) Distribution of a novel mutation in the first exon of the human dopamine receptor D4 gene in psychotic patients. Biol Psychiatry 34:459–464

Cichon S, Nöthen MM, Catalano M, DiBella D, Maier W, Lichtermann D, Minges J, et al (1995) Identification of two novel polymorphisms and a rare deletion variant in the human dopamine D4 receptor gene. Psychiatr Genet 5:97–103

Grice DE, Leckman JF, Pauls DL, Kurlan R, Kidd KK, Pakstis AJ, Chang FM, et al (1996) Linkage disequilibrium between an allele at the dopamine D4 receptor locus and Tourette syndrome, by the transmission-disequilibrium test. Am J Hum Genet 59:644–652

Hebebrand J, Nöthen MM, Lehmkuhl G, Poustka F, Schmidt M, Propping P, Remschmidt H (1993) Tourette's syndrome and homozygosity for the dopamine D3 receptor gene. Lancet 341:1483

Lichter JB, Barr CL, Kennedy JL, Van Tol HHM, Kidd KK, Livak KJ (1993) A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. Hum Mol Genet 2:767–773

Nöthen MM, Cichon S, Hemmer S, Hebebrand J, Remschmidt H, Lehmkuhl G, Poustka F, et al (1994*a*) Human dopamine D4 receptor gene: frequent occurrence of a null allele and observation of homozygosity. Hum Mol Genet 3:2207–2212

Nöthen MM, Hebebrand J, Knapp M, Hebebrand K, Camps A, von Gontard A, Wettke-Schäfer R, et al (1994*b*) Association analysis of the dopamine D2 receptor gene in Tourette's syndrome using the haplotype relative risk method. Am J Med Genet 54:249–252

Spielman RS, McGinnis RE, Ewens WJ (1993) Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). Am J Hum Genet 52:506–516

Van Tol HHM, Wu CM, Guan H-C, Ohara K, Bunzow JR, Civelli O, Kennedy J, et al (1992) Multiple dopamine D4 receptor variants in the human population. Nature 358:149–152

Address for correspondence and reprints: Dr. Johannes Hebebrand, Clinical Research Group, Department of Child and Adolescent Psychiatry, Philipp's University of Marburg, 35033 Marburg, Germany. E-mail: hebebran@post.med.uni-marburg.de
© 1997 by The American Society of Human Genetics. All rights reserved.
0002-9297/97/6101-0033$02.00

Am. J. Hum. Genet. 61:239–241, 1997

Exclusion of Atypical Vitelliform Macular Dystrophy from 8q24.3 and from Other Known Macular Degenerative Loci

To the Editor:

Atypical vitelliform macular dystrophy (VMD1; OMIM 153840) is an autosomal dominant disorder that can lead to blindness. VMD1 is characterized by complete penetrance but extremely variable expressivity, including with regard to age of onset and rate of progression. The findings for VMD1 include (1) macular and/or peripheral retinal lesions that may be small and yellow, intermediate and white, or large and depigmented, and (2) peripapillary abnormalities that are initially in the temporal nerve bundle but that progress circumferentially. The phenotype of VMD1 is similar to that of Best disease (VMD2; OMIM 153700); however, the macular lesions of VMD1 and VMD2 are clinically distinguishable (Mintz-Hittner et al. 1984).

An early linkage study in one large family reported linkage between the VMD1 locus and the soluble glutamate-pyruvate transaminase (GPT) locus, with a maximum two-point LOD score of 4.3 at 5% recombination (Ferrell et al. 1983). At that time, the GPT locus had been mapped tentatively to chromosome 16 (Wijnen and Meera Khan 1982). Recently, however, we have mapped the GPT locus to the long arm of chromosome 8 and have developed a PCR-RFLP assay for GPT typing (Sohocki et al. 1997). All previous GPT typing was by determination of the serologic phenotype only, and, because there are dramatic quantitative differences between the three common GPT serologic phenotypes (Welch 1972), GPT serotyping was difficult. Furthermore, within the last 4 years, several other loci associated with autosomal dominant macular degeneration (adMD) have been mapped to chromosomal sites (table 1). Given the refined localization of the GPT locus and given the additional mapped loci for adMD, it was important to reexamine the localization of the VMD1 locus in the previously studied family.

To further characterize the VMD1 locus, we recently