Eur Arch Psychiatry Clin Neurosci (1995) 245:50–52

ORIGINAL PAPER

Kenneth Blum · Peter J. Sheridan · Robert Wood
Eric R. Braverman

Dopamine D2 receptor gene polymorphisms in Scandinavian chronic alcoholics: a reappraisal

Received: 5 September 1994 / Accepted: 3 November 1994

The paper by Geijer et al. (1994) in European Archives of Psychiatry and Clinical Neuroscience, claiming a lack of association between the DRD2 TaqI A1 or B1 alleles and alcoholism, although on the surface appears to be correct, suggests after careful scrutiny of the data and statistical recalculation an opposite point of view.

Being well aware of the existing controversy with regard to association studies in the literature and the important need to characterize the chronicity and severity of alcoholics utilized in their study, the authors successfully differentiated a number of alcoholism subtypes in both living and autopsied specimens. To suggest that 56 of 74 inpatient alcoholics recruited from an inpatient alcohol detoxification program were assessed for severity according to the criteria of DSM-III-R and examination of all available hospital records is not acceptable because alcoholism severity cannot be determined by DSM-III-R alone without the aid of other more revealing instruments (i.e., MAST, SADQ, detailed drug and alcohol use profile questionnaires, structured interviews) utilized by other researchers also attempting to assess severity of alcoholism for similar association studies (Blum et al. 1991, 1992; Arinami et al. 1993; Parsian et al. 1991; Amadeo et al. 1993; Noble et al. 1994). Certainly, it is well established that the frequency of the DRD2 A1 allele decreases in a heterogeneous or mixed (less severe and severe alcoholics) population of alcoholics when compared with severe alcoholics (Blum et al. 1990, 1991, 1993; Noble et al. 1994; Arinami et al. 1993). We therefore suggest that the particularly low A1 allele frequency in Geijer's chronic alcoholics was due to possibly mixed, rather than true, severe alcoholics with associated medical complications (i.e., liver damage, cirrhosis, esophageal varicies, neuropathies, etc.) as reported in other studies where the DRD2 A1 allele frequency was significantly higher (Parsian et al. 1991; Blum et al. 1990, 1991, 1993, Noble et al. 1994; Arinami et al. 1993). However, it is very interesting that when Geijer and associates genotyped 19 deceased Caucasian alcoholics known to have alcohol-related tissue damage (liver, pancreas, central nervous system, stomach, kidneys, heart esophagus, and muscle), the allelic frequency increased to 47%. Moreover, as pointed out in their article, when they rated the tissue damage (light, moderate, or severe) they found that in 10 subjects having tissue damage > 10, the A1 allele increased to 60%, a finding similarly found by Parsian et al. (1991).

Additionally, the A1 allele of the DRD2 gene also increased in those inpatients having onset ≤ 25 years (up to 45% compared with only 22% in inpatients having onset > 25 years), consistent with other studies with regard to DRD2 A1 allelic association with age of onset of alcoholism (Arinami et al. 1993) and in polysubstance abuse (Comings et al. 1994), as well as in other nonmolecular genetic studies finding a correlation between age of onset of alcoholism and genetic or inheritable contribution (Irwin et al. 1990).

Another curious and somewhat disturbing aspect of the Geiger article is the number of control groups utilized for statistical comparisons. By subdividing these groups it tends to dilute sample size as well as power of analysis. In reviewing their control groups it is not obvious as to the rationale for evaluating controls without assessing for any DSM-III-R diagnosis as well as first- or second degree relatives with alcohol abuse or dependence. In fact, based on the number of additional positive association studies with regard to other addicitive/compulsive behaviors, i.e.,

Kenneth Blum (✉)
Department of Pharmacology,
University of Texas Health Science Center at San Antonio,
San Antonio, TX 7882884-7764, USA

Peter J. Sheridan
Department of Structural and Cellular Biology,
University of Texas Health Science Center at San Antonio,
San Antonio, TX 7882884-7764, USA

Robert Wood
Computing Resources,
University of Texas Health Science Center at San Antonio,
San Antonio, TX 7882884-7764, USA

Eric R. Braverman · Kenneth Blum
Department of Clinical Science, The PATH Foundation,
Princeton, NJ 08540, USA

polysubstance abuse (Smith et al. 1992; O'Hara et al. 1993; Noble et al. 1994; Comings et al. 1994), smoking (George et al. 1993; Noble et al. 1994; Comings et al. 1994), obesity (Blum et al. 1994; Noble et al. 1994; George et al. 1993), P300 wave activity (Johnson et al. 1992), attention-deficit/hyperactivity disorder (Comings et al. 1991), and Tourette's syndrome (Devor 1992; Comings 1992; Comings et al. 1991), among others, why did the authors only assess alcohol abuse and dependence excluding all other possible associated problems?

Taking all of the above into consideration, we decided to recalculate their data by combining a number of experimental and control groups. Because the authors stated that there was a tendency of increased DRD2 TaqI A1 or B1 allele frequencies in alcoholic groups selected for severity (i.e., severity according to DSM-III-R criteria and early onset of severe medical complications due to alcohol abuse), and decreased frequencies in the corresponding less severe alcohol group, we decided to combine the following groups: P3 = inpatients' onset ≤ 25 years (n = 29) with P5 = autopsied subjects with pathological, anatomical signs of alcoholism (n = 19); and C3 = controls screened for any DSM-III-R diagnosis and first-degree relatives with alcohol abuse or dependence (n = 52) with C4 = controls screened for any DSM-III-R diagnosis and first- or second-degree relatives with alcohol abuse or dependence (n = 40). Statistical analysis revealed no difference between P3 and P5 or C3 and C4; therefore, these groups were combined for subsequent analysis as severe and control groups, respectively. The resultant DRD2 allelic prevalence in these two groups are as follows: P3–5 = A1–21/38 (55.2%); C3–C4 = A1–24/92 (26%). Tesing for significance utilizing χ^2 test (Yates) revealed a significant difference (χ^2 = 8.87; df = 1; P = 0.003; OR = 3.5) between these two groups supporting an increased prevalence of the A1 allele in severe Scandinavian alcoholic probands compared with screened controls. Moreover, when we compared their P6 group (autopsied subjects, tissue damage < 10P (n = 10) against the combined C3 and C4 groups (n = 92), we found a significant association (Fischers exact one-tailed test; P < .035) between the TaqI A1 variant of the DRD2 gene and severe alcoholism similar to the previous work of Parsian et al. (1991) and Blum et al. (1990). Finally, when we compared C4 (n = 40) > C3 (n = 52) > P3 (n = 29) > P5 (n = 19) > P6 (n = 10) utilizing linear trend analysis, we found a progressive increase in A1+ allelic prevalence (25, 27, 45, 47, and 60%), with the A1+ allelic prevalence being significantly higher (χ^2 = 7.61; df = 4; P = 0.006) in the most severely damaged tissue group, supporting the view of TaqI A1 DRD2 gene association with severe alcoholism, confirming previous reports (Blum et al. 1990; see Fig. 1).

Some minor comments center around Geijer's decision to exclude probands without history of abuse or dependence of psychoactive substances other than alcohol from their study in light of the findings by others, particularly the work of Comings et al. (1994), who found increasing A1 allelic prevalence with an increased number of psychoactive drugs abused and decreasing A1 prevalence in alcoholics without comorbid drug abuse. Moreover, there was no mention of why there was no genotyping of TaqI B1 DRD2 in both P5 and P6 groups.

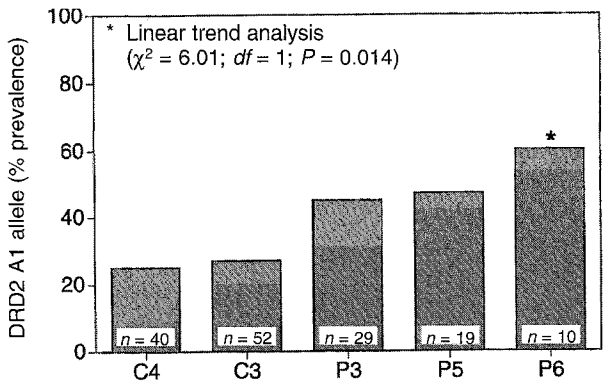

Fig. 1 Genotype distribution of the TaqI A1 allele of the DRD2 gene in the following groups: C4 (controls screened for any DSM-III-R diagnosis and first- or second-degree relatives with alcohol abuse or dependence); C3 (controls screened for any DSM-III-R diagnosis and first-degree relatives with alcohol abuse or dependence); P3 (inpatients onset ≤ 25 years); P5 (autopsied subjects with pathological, anatomical signs of alcoholism); and P6 (autopsied subjects, tissue damage < 10 score). The number of probands are indicated in *boxes*. Linear trend analysis revealed a significant effect (χ^2 = 6.01; df = 1; P = 0.014)

In summary, reappraisal of the Geijer paper based on our recalculation would counter their first interpretation favoring the more sanguine view that, although no significant differences between controls and alcoholics were observed with the DRD2 A1 allele, a significant increased A1+ allele frequency in alcoholic groups selected for severity (i.e., early onset or severe medical complications due to alcohol abuse) and decreased frequency in the corresponding less severe alcoholic group was found, supporting the involvement of the DRD2 gene in severe forms of alcoholism.

References

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders (DSM-III-R) 3rd edn, revised. American Psychiatric Association, Washington, DC

Amadeo S, Abbar M, Fourcade ML, Waksman G, Leroux MG, Madec A, Selin M, Champiat J-Claude, Brethome A, Lucclaire Y, Castelnau D, Venisse J-L, Mallet J (1993) D_2 dopamine receptor gene and alcoholism. J Psychiatr Res 27:173–179

Arinami T, Itokawa M, Komiyama T, Mitsushio H, Mori H, Mifune H, Hamaguchi H, Toru M (1993) Association between severity of alcoholism and the A1 allele of the dopamine D_2 receptor gene Taq1 a RFLP in Japanese. Biol Psychiatry 33: 108–114

Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, Nogami H, Briggs AH, Cohn JB (1990) Allelic association of human dopamine D_2 receptor gene in alcoholism. JAMA 263:2055–2060

Blum K, Noble EP, Sheridan PJ, Finley O, Montgomery A, Ritchie T, Ozkaragoz T, Fitch RJ, Sadlack F, Sheffield D, Dahlmann T, Halbardier S, Nogami H (1991) Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. Alcohol 8:409–416

Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Ozkaragoz T, Fitch RJ, Wood R, Finley O, Sadlack F (1993) Genetic predisposition in alcoholism: association of the D2 dopamine receptor TaqI B1 RFLP with severe alcoholism. Alcohol 10:59–67

Comings DE (1992) The D2 dopamine receptor and Tourette's syndrome. JAMA 267:652

Comings DE, Comings B, Muhleman D, Dietz G, Shahbahrami B, Tast D, Knell E, Kocsis P, Baumgarten R, Kovacs BW, Levy DL, Smith M, Borison RL, Evans D, Klein DN, MacMurray J, Tosk JM, Sverd J, Gysin R, Flanagan SD (1991) The dopamine D_2 receptor locus as a modifying gene in neuropsychiatric disorders. JAMA 266:1793–1800

Comings DE, MacMurray J, Johnson JP, Muhleman D, Ask MN, Ahn C, Gysin R, Flanagan SD (1994) The dopamine D2 receptor gene: a genetic risk factor in polysubstance abuse. Drug Alcohol Depend 34:175–180

Devor EJ (1992) The D2 dopamine receptor and Tourette's syndrome. JAMA 267:651–652

Geiger T, Neiman J, Rydberg U, Gyllander A, Jönsson L, Sedvall G, Valverius P, Terenjus L (1994) Dopamine D2 receptor gene polymorphisms in Scandinavian chronic alcoholics. Eur Arch Psychiatry Clin Neurosci 244:26–32

George SR, Cheng R, Nguyen T, Israel Y, O'Dowd BF (1993) Polymorphisms of the D4 dopamine receptor alleles in chronic alcoholism. Biochem Biophys Res Commun 196(1):107–114

Irwin M, Schuckit MA, Smitz TL (1990) Clinical importance of age at onset in type I and type 2 primary alcoholics. Arch Gen Psychiatry 47:320–324

Johnson JP, Kelley JT, Comings DE, Flanagan SD, Nessman DL, Tosk JM (1992) Genetic influence on the P300 latency in substance abusers. Clin Neuropsychol 6:344

Noble EP, Syndulko K, Fitsch RJ, Ritchie T, Bohlman MC, Guth P, Sheridan PJ, Montgomery A, Heinzmann C, Sparkes RS, Blum K (1994) D2 receptor Taq I A alleles in alcoholic and nonalcoholic patients. Alcohol Alcohol (in press)

O'Hara BF, Smith SS, Bird G, Persico A, Suarez B, Cutting GR, Uhl GR (1993) Dopamine D2 receptor RFLPs, Haplotypes and their association with substance use in black and caucasian research volunteers. Hum Hered 43:209–218

Parsian A, Todd RD, Devor EJ, O'Malley KL, Suarez BK, Reich T, Cloninger CR (1991) Alcoholism and alleles of the Human D_2 dopamine receptor locus. Arch Gen Psychiatry 48:655–663

Smith SS, O'Hara BF, Persico AM, Gorelick DA, Newlin DB, Vlahov D, Solomon L, Pickens R, Uhl GR (1992) The D_2 dopamine receptor Taq 1 B1 restriction fragment length polymorphism appears more frequently in polysubstance abusers. Arch Gen Psychiatry 49:723–727