Address for correspondence and reprints: Dr. Lionel C. C. Lim, Department of Psychological Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 0511, Republic of Singapore.

0002-9297/95/5704-0036$02.00

Am. J. Hum. Genet. 57:978, 1995

Reply to Nöthen et al.

To the Editor:

Lim et al. (1994) found a positive association between monoamine oxidase (MAO) gene and bipolar affective disorder by using a dinucleotide repeat polymorphism, and we have replicated their findings (Kawada et al. 1995). However, Nöthen et al. present data that do not support this association. Studies of Lim et al. (1994) and our own were based on case-control design, while the study of Nöthen et al. employed the haplotype relative risk (HRR) method. Obviously, HRR method is better than conventional case-control study because this method could overcome the problem of undetected population stratification, as Nöthen et al. clearly stated. Thus, the findings of Nöthen et al. seem to be more reliable than studies of Lim et al. and our own. However, this report is the first that does not support the association, and their evidence against the association is still weak because they also use the same intronic polymorphism as Lim et al. and Kawada et al. It would certainly be premature to conclude that the findings by Lim et al. and Kawada et al. occurred either as a result of population stratification or merely as a chance false positive. We agree with Nöthen et al that the association should be provable by direct examination of coding or regulatory sequences of the MAO gene.

YASUHARA KAWADA[1] AND SHIN NANKO[2]
[1]*Department of Psychiatry, Juntendo University School of Medicine, and* [2]*Department of Psychiatry, Teikyo University School of Medicine, Tokyo*

References

Lim LCC, Powell JF, Murray R, Gill M (1994) Monoamine oxidase A gene and bipolar affective disorder. Am J Hum Genet 54:1122-1124

Kawada Y, Hattori M, Dai XY, Nanko S (1995) Possible association between monoamine oxidase A gene and bipolar affective disorder. Am J Hum Genet 56:335-336

Address for correspondence and reprints: Dr. Shinichiro Nanko, Department of Psychiatry, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173, Japan.

0002-9297/95/5704-0037$02.00

Am. J. Hum. Genet. 57:978–979, 1995

Mutations in Galactosemia

To the Editor:

This Letter raises four issues concerning two papers on galactosemia published in the March 1995 of the *Journal.* First, table 2 in the paper by Elsas et al. incorrectly attributes seven galactose-1-phosphate uridyl transferase (GALT) mutations (S135L, L195P, K285N, N314D, R333W, R333G, and K334R). The table also fails to mention that others have reported the same two findings attributed to "Leslie et al. 1992; Elsas et al. 1993 and in press" and "Leslie et al. 1992; Elsas et al. 1994." The first finding on the prevalence of the Q188R galactosemia mutation in the G/G Caucasian population has also been described by Ng et al. (1994), and the second finding on the correlation of the N314D GALT mutation with the Duarte variant was reported by Lin et al. (1994). Second, Elsas et al. (1995) suggest that the E203K and N314D mutations may "produce intraallelic complementation when in *cis*" (p. 630). This speculation is supported by the activity data of individual III-2 (fig. 2, Elsas et al. [1995]) but is inconsistent with the activities of three other individuals I-1, II-1, and III-1 of the same pedigree (fig. 2, Elsas et al. [1995]). The GALT activity measured in these three individuals suggests a dominant negative effect of E203K in E203K-N314D chromosomes, since they all have less than normal activity. Thus, the preponderance of the data in this paper is at odds with the authors' speculation. It is worth recalling that Lin et al. (1994) also identified four N314D GALT mutations on 95 galactosemic chromosomes examined. A similar situation also appears to be the case in proband III-1 (with genotype E203K-N314D/IVSC, fig. 2) in the Elsas et al. (1995) paper.

Third, the paper on galactosemia in the March 1995 issue of the *Journal* by Fridovich-Keil et al. (1995) states that a paper by Reichardt et al. (1992) contains an "assumption" that "may require reconsideration" on galactosemia mutations (p. 645). The paper by Reichardt et al. (1992) in fact shows that nonconserved ("unimportant," according to Fridovich-Keil et al. [1995]) residues can be mutated to result in galactosemia (in this case the R148W mutation, which destabilizes the GALT protein). Finally, Fridovich-Keil et al. (1995) and Elsas et al. (1995) use the data we gathered with the mammalian expression system inconsistently. In one paper (Elsas et al. [1995]), the authors quote mammalian expression data when they support their point, but Fridovich-Keil et al. (1995) disregard the same data when they are at odds with their yeast system. A number of investigators (Banroques et al. [1983]; Reichardt [1991]) have documented full-length, immunoreactive GALT protein in all galactosemic patients they Western blotted. Fridovich-

Keil et al. (1995) have never shown the presence of any human GALT protein in their yeast system. Thus, the molecular bases of the phenotypes observed in the yeast expression system is unclear at this time. No reports on expression of the common N314D mutation in yeast have been published. However, Elsas et al. (1993) reported that "an evaluation of the N314D mutation in a yeast expression system is in progress." In fact, Dr. Elsas reported at a public session of this Society's annual meeting in 1993 that N314D in yeast encodes near normal activity. This finding is inconsistent with activity data for the Duarte variant that depresses GALT activity significantly in humans. It seems that the yeast expression system, while paralleling patient data in some cases, has not been proved yet to model human biochemical phenotypes faithfully. Clearly, this system can be used very elegantly as shown by Fridovich-Keil et al. (1995). It is also now well documented that the *cos* cell system can—on occasion—overestimate GALT (and other) activities (e.g., Ashino et al. [1995]). Fridovich-Keil et al. (1995) offer some possible explanations for this situation. It is, therefore, suggested that the two expression systems, mammalian and yeast, be used in parallel for all structure/function studies of the GALT enzyme, since both have their own strengths and weaknesses.

JUERGEN K. V. REICHARDT
Institute for Genetic Medicine and Department of Biochemistry and Molecular Biology
University of Southern California School of Medicine
Los Angeles

References

Ashino J, Okano Y, Suyama I, Yamazaki T, Yoshino M, Furuyama J-I, Lin H-C, et al. Molecular characterization of galactosemia (type 1) mutations in Japanese. Hum Mutat (in press)

Banroques J, Schapira F, Gregori C, Dreyfus JC (1983) Molecular studies on galactose-1-phosphate uridyltransferase from normal and mutant subjects. Ann Hum Genet 47:177–185

Elsas LJ, Dembure PP, Brown AL, Singh R, Fernhoff PM, Langley S, Hjelm N, et al (1993) A common mutation causing the Duarte galactosemia allele. Am J Hum Genet Suppl 53:A900

Elsas LJ, Langley S, Steele E, Evinger J, Fridovich-Keil JL, Brown A, Singh R, et al (1995) Galactosemia: a strategy to identify new biochemical phenotypes and molecular genotypes. Am J Hum Genet 56:630–639

Fridovich-Keil JL, Langley SD, Mazur LA, Lennon JC, Dembure PP, Elsas LJ II (1995) Identification and functional analysis of three distinct mutations in the human galactose-1-phosphate uridyltransferase gene associated with galactosemia in a single family. Am J Hum Genet 56:640–646

Lin H-C, Kirby LT, Ng WG, Reichardt JKV (1994) On the molecular nature of the Duarte variant of galactose-1-phosphate uridyl transferase (GALT). Hum Genet 93:167–169

Ng WG, Xu Y-K, Kaufman FR, Donnell GN, Wolff J, Allen RJ, Koritala S, et al (1994) Biochemical and molecular studies of 132 patients with galactosemia. Hum Genet 94:359–363

Reichardt JKV (1991) Molecular analysis of 11 galactosemia patients. Nucleic Acids Res 19:7049–7052

Reichardt JKV, Belmont JW, Levy HL, Woo SLC (1992) Characterization of two missense mutations in human galactose-1-phosphate uridyltransferase: different molecular mechanisms for galactosemia. Genomics 12:596–600

Address for correspondence and reprints: Dr. Juergen K. V. Reichardt, Department of Biochemistry and Molecular Biology, Institute for Genetic Medicine, University of Southern California School of Medicine, 2001 Zonal Avenue, HMR 413, Los Angeles, CA 90033.

0002-9297/95/5704-0038$02.00

Am. J. Hum. Genet. 57:979–980, 1995

Reply to Reichardt

To the Editor:

We thank Dr. Reichardt for carefully scrutinizing table 2 in Elsas et al. (1995) for attribution of mutations. He is concerned about the S135L mutation, which we attributed to Reichardt and Woo (1991) instead of Reichardt et al. (1992*b*). In Reichardt et al. (1992*b*), he describes the S135L as a "polymorphism" that "encodes almost normal activity" (pp. 5430–5431). Typographical errors did inadvertently attribute the R333G and K334R mutations to Reichardt (1992*a*) rather than to Leslie et al. (1992) and the L195P to Leslie et al. (1992) rather than to Reichardt et al. (1992*a*). In this dynamic field, it is sometimes difficult to acknowledge description of a given "mutation." For example, although N314D was identified in 1991 (Reichardt and Woo), it was first recognized as associated with the Duarte biochemical phenotype in 1992 (Leslie et al.), and its prevalence was defined in 1994 (Elsas et al.). Lin et al. (1994) confirmed its association with the Duarte phenotype and found four N314D alleles in 95 biochemically defined G-alleles, (Lin et al. [1994], table 1, p. 168). Lin et al. found no "additional nucleotide substitutions in the entire [galactose-1-phosphate uridyl transferase] GALT region" (p. 169). The article by Elsas et al. (1995) suggests that he missed non-Q188R G-alleles associated with the generally prevalent N314D allele (5.9% in the general population).

Reichardt requests clarification of our speculation that the E203K mutation may complement the N314D