Letters to the Editor

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Pseudoautosomal Marker DXYS20 and Manic Depression

To the Editor:

Yoneda et al. (1992) observed a significant association between manic-depressive illness and a 13.5-kb band of the pseudoautosomal marker DXYS20 (probe 362A) in *Eco*RI digests of 49 Japanese patients compared with 119 controls. The 13.5-kb allele was designated "A4 allele" and was found on at least one chromosome in 46.9% of the patients, compared with 26.1% of the controls. The relative risk of the A4 allele for the disease was 2.51. We have genotyped the *Eco*RI RFLP in 73 patients (40 females and 33 males) who fulfill DSM-III-R criteria of manic-depressive illness (bipolar affective disorder) and in 79 controls (34 females and 45 males). All subjects included in our study were unrelated and were of German descent.

We used the probe 3cos-PP, which, by sequence analysis, was shown to be directly homologous to the independently cloned probe 362A (Rappold et al. 1992). The pseudoautosomal locus DXYS20 represents a VNTR-like minisatellite, and many polymorphic bands are recognized by means of several restriction endonucleases (Page et al. 1987). In *Eco*RI digests, sizes of bands cluster, and we grouped our bands according to allele sizes used by Yoneda et al. In addition to the alleles reported by Yoneda et al., we observed a 10-kb band in five subjects.

Our results are shown in table 1. The frequency of the A4 allele did not differ significantly between patients (.35) and controls (.36) ($\chi^2 = 0.06$, $P > .05$). Thus, our data do not support a widespread or consistent association between DXYS20 and bipolar affective disorder.

Table 1

Presence or Absence of the A4 Allele at the DXYS20 Locus

Group	No. with A4 Allele	No. without A4 Allele	Total
Patients	42 (23)	31 (26)	73 (49)
Controls	45 (31)	34 (88)	79 (119)

NOTE.—Values in parentheses indicate nos. found by Yoneda et al. (1992).

A large degree of ethnic variation is seen with DXYS20 (Rappold et al. 1992) and might explain the difference of allele frequencies in controls from Japan and Germany. Since VNTRs evolve rapidly, they may not always be the best markers to detect disease associations, where a positive effect requires linkage disequilibrium. In any case, it should be useful to study larger samples of Japanese patients and controls to see whether the association holds true in the same ethnic population.

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MARKUS M. NÖTHEN,* SVEN CICHON,*
JEANETTE ERDMANN,*
JUDITH KÖRNER,† MARCELLA RIETSCHEL,†
GUDRUN A. RAPPOLD,‡
JÜRGEN FRITZE,§ AND PETER PROPPING*
Institute of Human Genetics, and †Department of Psychiatry, University of Bonn, Bonn; ‡Institute of Human Genetics, University of Heidelberg, Heidelberg; and §Department of Psychiatry, University of Würzburg, Würzburg

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Incorrect Genetic Counseling of a Couple with β-Thalassemia, Due to Incomplete Testing

To the Editor:

A few years ago an American couple of Italian descent, both with a distinct microcytosis and hypochromia and with a distant paternal relative with an undefined "thalassemia," sought family-planning advice. They were told that they could establish a family without fear of having a baby with β-thalassemia (β-thal) major, because the level of Hb A_2 was elevated only in the mother and not in the father (table 1). The available data were interpreted to indicate that the mother had a classical β-thal trait, while the father likely had one of the α-thal-1 deletions which are rare among Italians. Analysis of in vitro globin-chain synthesis was not performed.

Their only child came to our attention at the age of 10 mo. A striking anemia was observed, with severe microcytosis and hypochromia (Hb 7.1 g/dl, PCV 0.227 liter/liter, RBC 2.97×10^{12}/liter, MCV 76.4 fl, MCH 23.9 pg, and MCHC 31.3 g/dl), nucleated red cells, and clinical features of a β-thal major. Cation-exchange high-performance liquid chromatography (HPLC) (Bissé and Wieland 1988) gave the following Hb composition: Hb A 4.1%; Hb A_2 1.4%; and Hb F 94.5%, with a γ-chain composition of 16.5% $^{A}\gamma^{T}$; 60.1% $^{G}\gamma$, and 23.4% $^{A}\gamma$, determined by reversed-phase HPLC (Shelton et al. 1984). These results suggested a severe β-thal major.

Sequence analysis of amplified DNA (for methodology, see Gonzalez-Redondo et al. 1988, 1989) identified the father as a codon 39 (C → T) heterozygote, the mother as an IVS-I-110 (G → A) heterozygote, and the baby as a codon 39/IVS-I-110 compound heterozygote (the IVS-I-110 mutation is responsible for the small amount of Hb A in the infant). These results did not explain the low level of Hb A_2 in the father; neither did they explain the normal sequence data of the amplified δ-globin gene. However, gene-mapping analysis of genomic DNA with the enzymes *Hpa*I, *Hin*dIII, *Eco*RI, and *Bam*HI, by using the ψβ fragment as probe (for methodology, see Zeng et al. 1985), identified a 7.2-kb deletion with a 5′ breakpoint in the ψβ-δ intergenic region and a 3′ breakpoint in the second intervening region (IVS-II) of the δ-globin gene. These results are the same as those described by Galanello et al. (1990). This Corfu-type

Table 1

Hematologic Data

	Hb (g/dl)	PCV (liter/liter)	RBC (10^{12}/liter)	MCV (fl)	MCH (pg)	MCHC (g/dl)	Hb F (%)	Hb A_2 (%)
Father	12.5	.373	5.99	62.3	20.9	33.5	<.1	2.2
Mother	11.8	.368	5.59	64.9	21.1	32.5	1.8	5.2

NOTE.—Iron-deficiency anemia was excluded.