was found. These results would indicate an association between 362A(DXYS20) and bipolar disorder.

The pseudoautosomal region is the distal segment of the short arm of the sex chromosomes, where sequence homology and recombination take place between the X and Y chromosomes. This region is thought to contain a locus for susceptibility to bipolar disorder (Crow 1988). The gene for the Xg blood group, which was reported as being linked with bipolar disorder, is located near this region. The association we report here suggests a new region that could be investigated to identify the genetic basis of bipolar disorder by using other polymorphisms and linkage analysis.

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References

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3d ed. rev. American Psychiatric Association, Washington, DC

Baron M (1991) Genetics of manic depressive illness: current status and evolving concepts. In: McHugh PR, McKusick VA (eds) Genes, brain, and behavior. Raven, New York, pp 153–164

Crow TJ (1988) Sex chromosomes and psychosis: the case for a pseudoautosomal locus. Br J Psychiatry 153:675–683

Kelsoe JR, Ginns EI, Egeland JA, Gerhard DS, Goldstein AM, Bale SJ, Pauls DL, et al (1989) Reevaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. Nature 342:238–243

Leboyer M, Malafosse A, Boularand S, Campion D, Gheysen F, Samolyk D, Henriksson B, et al (1990) Tyrosine hydroxylase polymorphisms associated with manic-depressive illness. Lancet 335:1219

McGuffin P, Katz R (1986) Nature, nurture and affective disorder. In: Deakin JFW (ed) The biology of depression. Gaskell, London, pp 26–52

Mendlewicz J, Fleiss JL (1974) Linkage studies with X-chromosome markers in bipolar (manic-depressive) and unipolar (depressive) illnesses. Biol Psychiatry 9:261–294

Rouyer F, Simmler MC, Vergnaud G, Johnsson C, Levillers J, Petit C, Weissenbach J (1986) The pseudoautosomal region of the human sex chromosomes. Cold Spring Harb Symp Quant Biol 51:221–228

Woolf B (1955) On estimating the relation between blood group and disease. Ann Hum Genet 19:251–253

0002-9297/92/5105-0032$02.00

Am. J. Hum. Genet. 51:1173–1174, 1992

Missense Variations in the Cystic Fibrosis Gene: Heteroduplex Formation in the F508C Mutation

To the Editor:

Kobayashi et al. (1990) have described missense variations in the conserved region of exon 10 of the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene. In their paper, two ΔF508/F508C compound heterozygous individuals were reported. Clinical and epithelial physiological studies in both cases were normal, suggesting that the substitution of cysteine for phenylalanine at position 508, the F508C mutation, is benign. However, Kerem et al. (1990) reported a patient with this substitution who had typical symptoms of CF.

In routine ΔF508 mutation screening by visualization of the 3-bp deletion on a 12% polyacrylamide gel (Rommens et al. 1990), we detected an abnormal heteroduplex in the father of a CF patient of German origin. Subsequent direct sequencing of the PCR product confirmed that this clinically normal father is a compound heterozygote for the ΔF508/F508C mutations.

As shown in figure 1, this heteroduplex is slightly different from the usual heteroduplex in ΔF508 mutation carriers. Since the pattern of the ΔF508/F508C heteroduplex was not published, it is likely that similar cases can be overseen during the widely performed ΔF508 mutation screening by PAGE. Detection of more cases, such as the one presented here, together with careful, standardized clinical examination of the proband, would be valuable to verify the nature of this mutation.

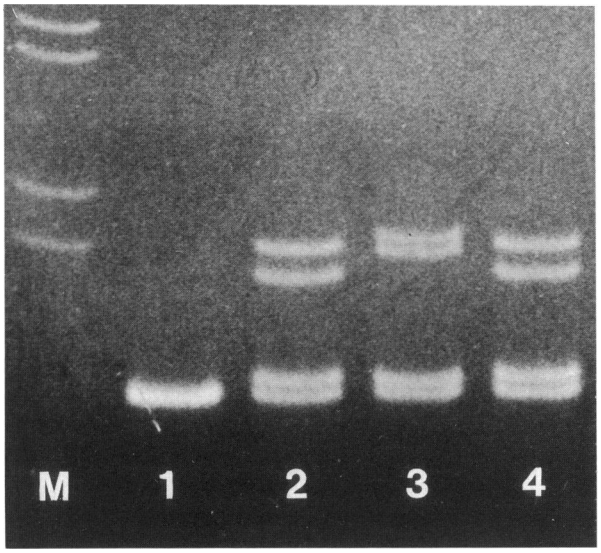

Figure 1 The 97-bp region, from CFTR gene exon 10, surrounding the ΔF508 deletion was amplified using primers described by Kerem et al. (1989), except that primer C16B was corrected to 5′-GTT TTC CTG GAT TAT GCC TGG CAC-3′. These primers were annealed at 52°C for 60 s, extended at 72°C for 90 s (with 1 unit of thermostable DNA polymerase), and denatured at 92°C for 60 s, in 30 cycles with a final 5-min extension. Ten microliters of amplification products from a 40-μl PCR reaction were visualized on a 16-cm 12% PAGE, as described by Rommens et al. (1990). The gel was run at 65 V for 12 h in a 1 × TBE (0.089 M Tris-borate, 0.089 M boric acid, and 0.002 M EDTA) buffer. PCR products from heterozygous ΔF508 mutation carriers are in lanes 2 and 4, and that from a homozygous patient is in lane 1. Lane 3 contains a PCR product from a ΔF508/F508C compound heterozygote individual with homoduplexes as in ΔF508 heterozygotes but with slightly different heteroduplexes. Both types of heteroduplexes comigrate with the 142-bp band of the 1-kb ladder DNA size marker from Gibco/BRL (lane M).

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References

Kerem B-s, Rommens JM, Buchanan J, Markiewicz D, Cox T, Chakravarti A, Buchwald M, et al (1989) Identification of the cystic fibrosis gene: genetic analysis. Science 245: 1073–1080

Kerem B-S, Zielenski J, Markiewicz D, Bozon D, Gazit E, Yahav E, Kennedy D, et al (1990) Identification of mutations in regions corresponding to the two putative nucleotide (ATP)-binding folds of the cystic fibrosis gene. Proc Natl Acad Sci USA 87:8447–8451

Kobayashi K, Knowles MR, Boucher RC, O'Brien WE, Beaudet AL (1990) Benign missense variations in the cystic fibrosis gene. Am J Hum Genet 47:611–615

Rommens J, Kerem B-S, Greer W, Chang P, Tsui L-C, Ray P (1990) Rapid nonradioactive detection of the major cystic fibrosis mutation. Am J Hum Genet 46:395–396

0002-9297/92/5105-0033$02.00