ORIGINAL ARTICLE

Linkage of Antisocial Alcoholism to the Serotonin 5-HT1B Receptor Gene in 2 Populations

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Background: In mice, quantitative trait locus studies and behavioral evaluation of animals deleted for 5-HT1B have implicated this serotonin autoreceptor in alcohol consumption and aggressive behavior. We therefore investigated whether the 5-HT1B gene *(HTR1B)* is linked to alcoholism with aggressive and impulsive behavior in the human, as represented by 2 psychiatric diagnoses: antisocial personality disorder and intermittent explosive disorder comorbid with alcoholism.

Methods: Linkage was first tested in 640 Finnish subjects, including 166 alcoholic criminal offenders, 261 relatives, and 213 healthy controls. This was followed by a study in a large multigenerational family derived from a Southwestern American Indian tribe (n = 418) with a high rate of alcoholism. All subjects were psychiatrically interviewed, blind-rated for psychiatric diagnoses, and typed for a *HTR1B G861C* polymorphism and for a closely linked short-tandem repeat locus, *D6S284*. Linkage was evaluated in sib pairs, and by using an association approach in which pedigree randomization corrects for nonindependence of observations on related subjects.

Results: In Finnish sib pairs, antisocial alcoholism showed significant evidence of linkage to *HTR1B G861C* ($P = .04$) and weak evidence with *D6S284* ($P = .06$). By association analysis, the 183 Finnish antisocial alcoholics had a significantly higher *HTR1B-86IC* allele frequency than the other 457 Finns we studied ($P = .005$). In the Southwestern American Indian tribe, significant sib pair linkage of antisocial alcoholism to *HTR1B G861C* ($P = .01$) was again observed, and there was also significant linkage to *D6S284* ($P = .01$).

Conclusion: These results suggest that a locus predisposing to antisocial alcoholism may be linked to *HTR1B* at 6q13-15.

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ALCOHOLISM IS a common,[1,2] debilitating,[3] genetically influenced,[3-7] and heterogeneous[6-9] disorder. Annually, approximately 100 000 deaths in the United States are attributable to alcohol abuse and alcoholism, making them the fourth leading cause of mortality after heart disease, cerebrovascular disease, and cancer.[10]

Adoption studies have identified a subtype of alcoholism characterized by high heritability and aggressive and impulsive personality.[6,7,11,12] This type of alcoholism is severe, relatively independent of environmental factors, and often associated with criminal behavior.[6,7,12] Numerous studies have reported reduced brain serotonin function in patients with this type of alcoholism. Specifically, low cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid, the major metabolite of serotonin, has been found in early-onset antisocial alcoholics,[13] impulsive alcoholic criminals,[14-16] and alcoholic fire setters.[16,17] Research on this form of alcoholism may enable some of the genetic components of this complex disorder to be identified and facilitate the development of more efficacious treatments and prevention strategies.

Molecular and statistical genetic studies on animal models have implicated the serotonin autoreceptor 5-HT1B *(Ht1b)* in the control of alcohol intake and aggression. First, an alcohol preference locus has been mapped in mice to the region where *Htr1b* is located.[18] Second, mice without the 5-HT1B receptor gene (herewith referred to as 5-Ht1b knockout mice) were found to have enhanced aggressive behavior. After an isolation period of 4 weeks, these gene knockout mice attacked intruders placed into their cages with shorter latency, higher frequency, and greater intensity than wild-type mice or heterozygous animals.[19] Third, the 5-Ht1b knockout mice show increased spontaneous alcohol consumption.[20]

PATIENTS AND METHODS

FINNISH SAMPLE

The Finnish sample consisted of Finnish alcoholic criminal offenders, their relatives, and population controls. The index cases were 166 male alcoholic criminals who, because of the nature of their crimes, were remanded to forensic psychiatric examination at the time of their initial incarceration. Additionally, 110 female and 151 male relatives were ascertained in 72 families through the index cases. Individuals with major psychotic episodes were excluded from the study. The population control sample consisted of 213 unrelated psychiatrically interviewed healthy Finnish male volunteers who were recruited by advertisements in local newspapers and paid for their participation. Population controls were in good general health, as established by physical examination, normal erythrocyte and lymphocyte indexes, liver enzyme and thyroid hormone levels, and serum electrolyte and creatinine concentrations. The Structured Clinical Interview for *DSM-III-R*[24-26] was administered by psychiatrists (H.N., M.E.). Psychiatric diagnoses were independently blind-rated from the interview data by the 2 research psychiatrists under the supervision of a senior research psychiatrist (G.L.B), who settled any disagreements. To maintain reasonable continuity with diagnostic practices in our previous studies, intermittent explosive disorder was diagnosed according to *DSM-III* criteria, which, unlike *DSM-III-R*, allows this diagnosis to be made even if the symptoms occurred when the subject was under the influence of alcohol. In the alcoholic subjects in the Finnish sample, the most common disorders were personality disorders (55.0%), substance-related disorders (23.9%), mood disorders (17.1%), and anxiety disorders (11.1%). This protocol was approved by the institutional review board of the National Institutes of Health, Bethesda, Md, and the National Institute of Mental Health, Bethesda, by the Office for Protection From Research Risks, Bethesda, by the University of Helsinki Department of Psychiatry institutional review board, Helsinki, Finland, and by the University of Helsinki Central Hospital institutional review board. All subjects provided informed consent before entering the study. All the subjects were 17 years or older at the time of the psychiatric interview. An additional 9 DNA samples were available from noninterviewed family members and were used to determine allele sharing proportions of sib pairs.

SOUTHWESTERN AMERICAN INDIAN SAMPLE

The Southwestern American Indian sample (n = 418) was collected for a family-based study on alcoholism and related psychiatric disorders. Because of the high prevalence of alcoholism, there was no need to ascertain subjects through affected probands, and the recruitment was blind to the clinical histories of subjects or their relatives. Use of the tribal name and exact reservation location is avoided because these details are unnecessary for the analyses set out here. Elder tribal members who were considered matriarchs or patriarchs and who possessed a good knowledge of family structures provided information on large multigenerational genealogies. Participants were genealogy members, older than 21 years, in general good health, and eligible for tribal enrollment (one-fourth tribal heritage). A total of 418 individuals belonging to the multigenerational family were interviewed. The Schedule for Affective Disorders and Schizophrenia–Lifetime Version[27] was administered to all subjects by a psychologist experienced in psychiatric assessment with this tribe and other American Indian populations (R.W.R.). Blind-rated diagnoses for alcoholism and other psychiatric disorders were based on (1) semistructured psychiatric interview with the Schedule for Affective Disorders and Schizophrenia–Lifetime Version and following the operationally defined criteria by Spitzer et al[28]; (2) medical, educational, court, and other records; and (3) corroborative information from family members. Antisocial personality disorder was diagnosed according to the Research Diagnostic Criteria.[28] Because of high rates of unemployment, participants were questioned in detail about the specific circumstances that may have contributed to their unemployment status. Diagnoses were made from the data by 2 blind raters: a clinical social worker and a clinical psychologist. Diagnostic differences were resolved in a consensus conference that included a senior psychiatrist experienced in diagnosis in American Indian people. In the alcoholics in the Southwestern Indian sample, the most common disorders were substance-related disorders (50.2%), mood disorders (29.9%), anxiety disorders (27.1%), and personality disorders (23.0%). Genotyping was performed by a technician who was blind to the phenotypic information. An additional 12 DNA samples were available from noninterviewed family members and were used to determine allele sharing proportions of sib pairs. This protocol was approved by the Tribal Council, and by the institutional review board of the National Institute of Alcohol Abuse and Alcoholism, National

In this study, we examined the role of the human *HTR1B* gene in vulnerability to alcoholism associated with aggressive and impulsive behavior as represented by the diagnoses of antisocial personality disorder and intermittent explosive disorder. Both of these disorders are characterized by destructive, impulsive, and aggressive behavior[21] and are associated with low levels of cerebrospinal fluid 5-hydroxyindoleacetic acid.[14-16] In addition, we have found that these diagnoses co-occur in families, suggesting an underlying basis for these disorders, which is at least in part shared (see below). These indi viduals are hereafter referred to as *antisocial alcoholics*.

Linkage and association were evaluated in 2 independent populations. The Finnish sample consisted of alcoholic criminal offenders, their family members, and population controls. The Southwestern American Indian sample was a multigenerational family derived from a tribe with a high rate of alcoholism. To test for linkage between the *HTR1B* gene and alcoholism, 2 marker loci were typed: *G861C* polymorphism within the *HTR1B* sequence[22] *(HTR1B G861C)* and a closely linked dinucleotide repeat locus, *D6S284*.[23]

Institutes of Health. All subjects provided informed consent before entering the study.

DIAGNOSTIC CATEGORIES

Three diagnostic categories were selected for analysis: antisocial alcoholism, nonantisocial alcoholism, and unaffected. Antisocial alcoholism required a diagnosis of *DSM-III-R* alcohol dependence or abuse and a diagnosis of antisocial personality disorder or intermittent explosive disorder. Nonantisocial alcoholism required *DSM-III-R* alcohol dependence or abuse without antisocial personality disorder or intermittent explosive disorder.[21] Unaffected status required that alcohol abuse, alcohol dependence, intermittent explosive disorder, and antisocial personality disorder all not be present. Diagnostic categorization in the American Indian study was the same as for the Finnish sample, except that antisocial alcoholism was defined by antisocial personality disorder and alcohol dependence or abuse. This modification was necessary because the Schedule for Affective Disorders and Schizophrenia–Lifetime Version interview instrument does not include the diagnosis of intermittent explosive disorder. All classifications were completed before the genetic analyses (**Table 1**).

GENOTYPING OF *HTR1B G861C* AND *D6S284*

The *HTR1B G861C* polymorphism can be typed by polymerase chain reaction, enzyme digestion, and gel electrophoresis, as described previously.[22] The *HTR1B* alleles are designated *HTR1B-861G* and *HTR1B-861C*. Primers were 5HT1B5 (5′GAA ACA GAC GCC CAA CAG GAC-3′) and 5HT1B6 (5′CCA GAA ACC GCG AAA GAA GAT-3′). The resulting product of polymerase chain reaction (548 base pairs [bp]) was digested with H*inc*II, which cuts it into 2 fragments of 452 and 96 bp when guanine is present at nucleotide 861 and into 3 fragments of 142, 310, and 96 bp if cytosine is present at this position. The frequency of the *HTR1B-861C* was 0.23 in the Finnish population control sample. In the American Indian sample, the frequency of *HTR1B-861C* was 0.62. Genotype distributions in both populations were consistent with Hardy-Weinberg expectations.

A flanking dinucleotide repeat sequence *D6S284*,[23] mapped[22] 9 centimorgans (cM) from *HTR1B G861C*, was typed by means of an automated DNA sequencer and fluorescent dye–labeled primers. Primers to amplify *D6S284* were 5′CAT GGC TGT CTA TCA AAC CC-3′ and 5′AAG CAT TTG TGT GGC TCT TG-3′. For each 15-µL polymerase chain reaction, 50 ng of genomic DNA was amplified in the presence of 200-µmol/L deoxyribonucleoside-5′-triphosphates (dNTPs) (Promega Corp, Madison, Wis), 10-mmol/L Tris hydrochloride (pH 8.3), 5-mmol/L potassium chloride, 2.0-mmol/L magnesium chloride, 0.25 U of *Taq* polymerase, and 0.33-µmol/L fluorescently labeled upstream primer and unlabeled downstream primer (Bioserve Biotechnologies, Laurel, Md). Polymerase chain reaction products were electrophoresed in the presence of an internal standard (Genescan 500, Applied Biosystems Inc, Foster City, Calif), on 6% acrylamide 5-mol/L urea denaturing gel and using a DNA sequencer (373A, Applied Biosystems Inc). The Bioautograph program (version 1.1, available from J.C.L.) was used to correct for gel shifts and to group measured sizes into discrete categories corresponding to 2-bp intervals. For *D6S284*, 11 alleles were detected in the Finnish sample, with an average heterozygosity of 0.711; in the American Indian sample, 8 alleles were detected, with an average heterozygosity of 0.620. Allele frequencies were in accordance with Hardy-Weinberg expectations in both populations.

STATISTICAL ANALYSIS

Sib Pair Linkage

Linkage analysis was conducted by means of the Haseman-Elston sib pair method.[29,30] With this method, the squared trait difference between siblings is regressed on the estimated proportion of marker alleles shared identical by descent. A negative slope is taken as evidence of linkage. Since the accuracy of sib pair linkage analysis depends on large sampling approximations, *P* values were verified by computer simulations. While the phenotype, family structures, and genotype distribution were held constant, the various *HTR1B* and *D6S284* alleles were randomly assigned to the founders of the pedigrees on the basis of their population frequencies. These simulated genotypes were subsequently transmitted to the offspring and analyzed for sib pair linkage by means of the SAGE Sibpal module.[30] By replicating this 10 000 times, a new empirical distribution was created that was used to obtain the *P* values presented in this study.

Association Study

Association was measured by a contingency table χ^2 statistic. An empirical sample distribution for this statistic was generated as follows. First, population allele frequencies were estimated from the sample. Then, genotype for the pedigree founders were simulated on the basis of the population frequencies. These genotypes were subsequently transmitted to the offspring, and the contingency table χ^2 statistic was computed for the simulated data set. By replicating these steps a large number (>1000) of times, a null distribution for the χ^2 statistic was generated. This was subsequently used to determine the significance of observations in the original contingency table. Nonrelated individuals were treated as pedigrees of size 1.

RESULTS

FAMILIALITY OF INTERMITTENT EXPLOSIVE DISORDER AND ANTISOCIAL PERSONALITY DISORDER

Familial co-occurrence of intermittent explosive disorder and antisocial personality was estimated in the Finnish alcoholic families. The rate of intermittent explosive disorder was 15.0% in the first-degree relatives of the index cases with antisocial personality disorder. In the population control sample consisting of unrelated healthy males (n = 213), antisocial personality disorder or intermittent explosive disorder was not observed.

SIB PAIR LINKAGE ANALYSIS

Modest evidence of linkage between antisocial alcoholism and both *HTR1B G861C* ($P = .04$) and *D6S284* ($P = .06$) was detected in the Finnish sib pairs. However, neither locus showed evidence of linkage to nonan-

Table 1. Distribution of Antisocial Alcoholics, Nonantisocial Alcoholics, and Unaffected Subjects in Finnish and Southwestern American Indian Samples

	Finnish Population, No.					Southwestern American Indian Tribe, No.		
	Index Cases	Male Relatives	Female Relatives	Population Controls	Total	Men	Women	Total
Antisocial	137	43	3	0	**183**	44	20	**64**
Nonantisocial	29	48	11	9	**97**	117	110	**227**
Unaffected	0	61	95	204	**360**	18	109	**127**
Total	**166**	**152**	**109**	**213**	**640**	**179**	**239**	**418**

tisocial alcoholism or the combination of antisocial and nonantisocial alcoholism. Analysis of the American Indian sample closely matched the findings in the Finns. Sib pair analysis showed positive evidence of linkage to antisocial alcoholism at both *HTR1B G861C* ($P = .01$) and *D6S284* ($P = .01$), and neither locus showed evidence of linkage to nonantisocial alcoholism or to the combination of antisocial alcoholism and nonantisocial alcoholism (**Table 2**).

ASSOCIATION ANALYSIS

In the Finnish sample, the frequency of the *HTR1B-861C* allele in antisocial alcoholic subjects was first evaluated by comparing the antisocial alcoholics (n = 183) with the rest of the individuals (n = 457) in this sample, including unaffected subjects and nonantisocial alcoholic subjects. A significant association was observed ($P = .005$). Further analyses showed that antisocial alcoholic subjects had a significant excess of the *HTR1B-861C* allele as compared with 360 unaffected subjects ($P = .02$) or with 97 nonantisocial alcoholic subjects ($P = .01$). Nonantisocial alcoholic subjects did not differ significantly from the rest of the sample or when compared with unaffected subjects alone. In the Southwestern American Indian tribe, *HTR1B G861C* was not associated to antisocial alcoholism, to nonantisocial alcoholism, or to these 2 subtypes of alcoholism combined (**Table 3**).

Table 2. Sib Pair Linkage Analysis of *HTR1B G861C* and *D6S284* to Antisocial Alcoholism in the Finnish Families and in the Southwestern American Indian Tribe*

	HTR1B G861C		*D6S284*	
Pairs	No.	Sharing IBD	No.	Sharing IBD
Finnish Families				
Unaffected	220	0.501	198	0.489
Discordant	79	0.459	85	0.434
Affected	51	0.504	41	0.510
	df = 159, slope = −0.213, *P* = .04		*df* = 146, slope = −0.137, *P* = .06	
Southwestern American Indian Tribe				
Unaffected	223	0.497	221	0.506
Discordant	71	0.421	63	0.404
Affected	11	0.603	10	0.632
	df = 180, slope = −0.312, *P* = .01		*df* = 161, slope = −0.238, *P* = .01	

**Unaffected, discordant, and affected refer to sib pairs in which neither sibling has the trait, only 1 sibling has the trait, and both siblings have the trait, respectively. No. is the number of sib pairs;* df *is the effective degrees of freedom, corrected for multiplex sibships, for the regression analysis; slope is the slope of the regression line; sharing IBD is the proportion of alleles identical by descent shared by sib pairs;* P *is the sib pair linkage* P *value. For each locus or population pair, IBD sharing is substantially less than 50% in the discordant sib pairs, thus suggesting that these pairs were most informative for the regression analysis.*

COMMENT

The major finding in this study is genetic linkage of *HTR1B G861C* polymorphism on chromosome 6q13-15 to antisocial alcoholism in Finns. This finding was supported by significant evidence of linkage between antisocial alcoholism and a dinucleotide repeat polymorphism *(D6S284)* closely linked to *HTR1B G861C*.[22] Moreover, both *HTR1B G861C* and *D6S284* showed significant evidence of linkage to antisocial alcoholism in the American Indian sample. The observed *P* values would not be sufficient to be considered positive in a high-density genome-wide scanning study with random markers.[31] However, such an analysis was not conducted here, but instead our findings are based on a candidate gene approach. Furthermore, the sib pair linkage *P* values were verified with computer simulations to control for type I errors. This is important because we have observed that sib pair linkage analysis can sometimes inflate *P* values if relatively small sample sizes are used, or if the trait is infrequent (data not shown). To further evaluate the role of *HTR1B* in vulnerability to antisocial alcoholism, we tested for association (ie, linkage disequilibrium) between *HTR1B G861C* and phenotypic categories by means of a simulation-based strategy that simultaneously uses both related and unrelated individuals. Association analysis in the Finnish sample showed that allele *HTR1B-861C* is overrepresented in antisocial alcoholic subjects, contributing to a small but significant increase in risk to that behavior (odds ratio, 1.55).

On the basis of these results, cautious inferences on the localization of the predisposing locus can be made. The *HTR1B G861C* polymorphism is unlikely to be the predisposing locus, since both alleles encode valine,[22] and there was no evidence of association in the Southwestern American Indian samples. Also, the coding se-

Table 3. Association of *HTR1B* Alleles With Alcoholism in Finnish and Southwestern American Indian Samples*

	No.	*HTR1B* - *861G*	*HTR1B* - *861C*
Finnish Population			
Antisocial alcoholic subjects vs nonantisocial alcoholic subjects + unaffected			
Antisocial	183	250 (0.68)	116 (0.32)
All others	457	703 (0.77)	211 (0.23)
		χ^2_1 = 10.18, simulation-derived χ^2 *P* = .005; OR, 1.55; 95% CI, 1.17-2.04	
Antisocial alcoholic subjects vs unaffected			
Antisocial	183	250 (0.68)	116 (0.32)
Unaffected	360	550 (0.76)	170 (0.24)
		χ^2_1 = 8.17, simulation-derived χ^2 *P* = .02; OR, 1.50; 95% CI, 1.12-2.00	
Antisocial alcoholic subjects vs nonantisocial alcoholic subjects			
Antisocial	183	250 (0.68)	116 (0.32)
Nonantisocial	97	153 (0.79)	41 (0.21)
		χ^2_1 = 7.01, simulation-derived χ^2 *P* = .01; OR, 1.73; 95% CI, 1.13-2.66	
Southwestern American Indian Tribe			
Antisocial alcoholic subjects vs nonantisocial alcoholic subjects + unaffected			
Antisocial	64	51 (0.40)	77 (0.60)
All others	354	267 (0.38)	441 (0.62)
		χ^2_1 = 0.21, χ^2 *P* = .65, nonsignificant; OR, 0.91; 95% CI, 0.61-1.37	
Antisocial alcoholic subjects vs unaffected			
Antisocial	64	51 (0.40)	77 (0.60)
Unaffected	127	100 (0.40)	154 (0.60)
		χ^2_1 = 0.01, χ^2 *P* = .92, nonsignificant; OR, 0.98; 95% CI, 0.62-1.55	
Antisocial alcoholic subjects vs nonantisocial alcoholic subjects			
Antisocial	64	51 (0.40)	77 (0.60)
Nonantisocial	227	167 (0.37)	287 (0.63)
		χ^2_1 = 0.40, χ^2 *P* = .53, nonsignificant; OR, 0.88; 95% CI, 0.58-1.34	

**Numbers under* HTR1B-861G *and* HTR1B-861C *refer to the number of chromosomes with particular alleles. Numbers in parentheses are allele frequencies. OR indicates odds ratio; CI, confidence interval.*

quence of *HTR1B* is unlikely to harbor the predisposing allele. First, *HTR1B* is a short (1137 bp) and intronless gene,[32,33] and therefore a stronger association finding would be likely if the predisposing allele resided within the *HTR1B* coding sequence. Second, 2 recent *HTR1B* mutation screening studies concluded that no common coding sequence functional variants exist.[22,34] The association between *HTR1B G861C* and antisocial alcoholism in the Finnish sample could be caused by a functional regulatory sequence polymorphism located several kilobases outside of the coding sequence. The polymorphism could, for example, alter the expression of the 5-HT1B receptor and, subsequently, central serotonin turnover. In the Southwestern American Indian sample, however, there was no evidence of association between antisocial alcoholism and *HTR1B G861C*. Since linkage disequilibrium is influenced by several other mechanisms besides recombination, including mutation, drift, breeding system, and selection, lack of association cannot be taken as a lack of linkage. For example, Thompson et al[35] showed that the power to detect linkage disequilibrium greatly depends on the allele frequencies of the loci, and whether the alleles of high and low frequency are in the same chromosomal phase. In the Finnish sample, the rare allele (q = 0.23) *HTR1B-861C* was associated with antisocial alcoholism, while in the Southwestern American Indian sample this particular allele was more common (q = 0.62), causing considerable reduction in power to detect linkage disequilibrium in this population. It is also possible that the association in the Finnish sample was caused by linkage disequilibrium between *HTR1B G861C* and some other gene within 6q13-15. At this time, 2 genes of interest are known to be located within the 6q13-15 region: cannabinoid receptor[36] and serotonin 5-HT1E receptor (*HTR1E*).[37] On the basis of the data published by Hoehe et al[36] and Lappalainen et al,[22] *HTR1B* and the cannabinoid receptor gene appear to be separated by a considerable distance. For example, *D6S26* was mapped 11 cM from cannabinoid receptor but only 3 cM from *HTR1B*. Also, *HTR1E* appears to be an unlikely site for functional variation causing predisposition to antisocial alcoholism. First, Shimron-Abarbanell et al[37] screened a large sample of whites for genetic variation within *HTR1E* and concluded that no common functional variation exists within this gene. Second, we have typed a relatively common silent substitution[37] within *HTR1E* in a large number of Finns and analyzed for linkage disequilibrium between *HTR1E* and *HTR1B*. We found no evidence of linkage disequilibrium between these genes (unpublished data, 1997).

In this study, a diagnosis of antisocial personality disorder or intermittent explosive disorder was used to identify alcoholic subjects with a more aggressive, impulsive form of this complex disorder who are more likely to have abnormal brain serotonin turnover. To further evaluate whether these 2 disorders share a common background, we estimated the co-occurrence of antisocial personality disorder and intermittent explosive disorder in Finnish alcoholic families. We found that the rate of intermittent explosive disorder was 15.0% in the first-degree relatives of the index cases with antisocial personality disorder. In the population control sample consisting of unrelated healthy males (n = 213), intermittent explosive disorder was not observed, consistent with the rarity (<1%) of disorders of impulse control in the general population.[38] Therefore, the risk ratio (λ) in the first-degree relatives of individuals with antisocial personality disorder

is greater than 15, suggesting an underlying basis for these disorders that is, at least in part, shared.

Taken together, these results from 2 unrelated population samples strongly suggest that a genetic variant that predisposes to antisocial alcoholism resides close to the *HTR1B* coding sequence, and indicate that 5-HT1B receptors may be involved in the control of aggression and impulsivity in humans.

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