Evidence of an Association Between the Vasopressin V1b Receptor Gene (AVPR1B) and Childhood-Onset Mood Disorders

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Context: Disturbances in stress hormones have been implicated in mood disorders, in particular in the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Arginine vasopressin (AVP) plays a crucial role in modulating the HPA axis under stress and does so through a G protein–coupled receptor, vasopressin V1b receptor (AVPR1b).

Objective: To determine if genetic variation in AVPR1B could be contributing to vulnerability to mood disorders.

Design: We genotyped single nucleotide polymorphisms (SNPs) across the AVPR1B gene in a family-based sample with childhood-onset mood disorders. Six SNPs were genotyped; 2 were novel nonsynonymous polymorphisms, and the other 4 were constituents of a haplotype that was previously shown to be protective against depression.

Setting: Twenty-three mental health facilities in Hungary.

Participants: The sample was composed of 382 Hungarian nuclear families ascertained through affected probands with a diagnosis of childhood-onset mood disorder.

Main Outcome Measures: Association with childhood-onset mood disorders was tested using the transmission disequilibrium test, which measures the transmission frequency of alleles, or haplotypes, from parents to affected offspring.

Results: Two of the AVPR1B SNPs showed association individually (Lys65Asn: $\chi^2 = 7.81$, $P = .005$; S4: $\chi^2 = 4.58$, $P = .03$); of particular interest is Lys65Asn, which causes an amino acid change in an intracellular protein domain. Haplotype analysis demonstrated significant overtransmission of the most frequent haplotype ($\chi^2 = 22.42$, $P < .001$). Furthermore, stratifying the sample by sex established that the association was predominantly in affected females, which is consistent with previous observations.

Conclusions: We have found evidence to implicate the AVPR1B gene in the etiology of mood disorders, particularly in females. Antagonists of AVPR1b exhibit antidepressant qualities; hence, genetic variation in AVPR1B may have implications in HPA axis dysregulation in mood disorders.

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The hypothalamic–pituitary–adrenal (HPA) axis is a neuroendocrine system that is integral to an individual’s response to stress. The primary hormones in the system are corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which work synergistically to stimulate the release of pituitary corticotropin. The end product of the cascade is glucocorticoid hormone (cortisol in humans), and its release from the adrenal cortex is regulated through a negative feedback mechanism. Dysregulation of the HPA is observed in approximately 50% of patients with depression and is said to be the most consistent biological observation in patients with mood disorders. However, studies investigating alterations in the HPA axis in children and adolescents with depressive symptoms are less consistent, with some finding no difference between patients and control groups in basal cortisol levels and response to CRH or dexamethasone hydrochloride challenge. Although most of these studies measured the response of the HPA axis to physiologic challenge (eg, dexamethasone suppression test [DST]), recently researchers have investigated the stress reactivity of the HPA axis to psychosocial stimuli and were able to detect alterations in children who are at high risk of developing depression and who were clinically depressed. This form of stressor is perhaps more representative of stress associated with everyday life compared with measuring the response of the HPA axis to a synthetic biochemical stimulator (eg, dexamethasone hydrochloride challenge).
methasone); such contextual differences could explain the opposing results seen between different stressors in childhood. Furthermore, in adults the DST was found to be more sensitive if used in combination with CRH (80% sensitivity) compared with dexamethasone alone (40% to 50% sensitivity), thus, previous studies of the DST in children using small sample sizes may be deficient in both power and sensitivity to detect alterations in the activation of the HPA axis.

The main activator of the HPA axis is CRH, which together with AVP stimulates the release of corticotropin. Under chronic stress, AVP expression in the paraventricular nucleus is enhanced and AVP becomes the primary activator of corticotropin. Vasopressin has been suggested to play the role of integrator between the behavioral and neuroendocrine responses to stress. The involvement of the vasopressinergic system in depression was first hypothesized by Gold et al. through observations of altered behavior in animal models after administration of vasopressin.

Arginine vasopressin is a nonapeptide produced in the hypothalamus with numerous functions aside from its role in the HPA axis, including osmoregulation, neurotransmission, and vascular constriction. Arginine vasopressin maintains these diverse roles through the recruitment of 3 distinct G protein-coupled receptors. The vasopressin V1b (AVPR1b) receptor is important in regulating pituitary corticotrophs’ responsiveness to vasopressin; on binding to the AVPR1b receptor, AVP activates phosphatidylinositol hydrolysis, which mobilizes intracellular Ca²⁺.

A positive correlation exists between changes in pituitary AVPR1b receptor levels and corticotropin responsiveness under chronic stress. Up-regulation of the AVPR1b receptor has been suggested in depression, which could contribute to the shift in the hypothalamic drive from CRH to AVP. During the chronic stress response, a rapid increase occurs in AVPR1B messenger RNA in the pituitary, which is driven by an elevation in glucocorticoid levels. Glucocorticoids interact directly with the AVPR1b receptor, increasing coupling to phospholipase C; this response enables the AVPR1b-stimulated release of corticotropin to be resilient to high levels of circulating glucocorticoids and the consequential down-regulation of vasopressin under times of stress.

Loss-of-function animal models support an integral role for the AVPR1b receptor in the stress response of the HPA axis. Mice that lack the AVPR1b receptor (V1bR−/−) exhibit a blunted HPA axis both at the basal level and under stressful conditions. Furthermore, Itoh et al. found differences in catecholamine release between wild-type and V1bR−/− mice, implying that AVPR1b is involved in stress-induced catecholamine release from the adrenal cortex.

Antagonists of AVP receptors have the potential to serve as therapeutic agents in treating depression and anxiety. An antagonist with dual affinities for the AVPR1a and AVPR1b receptor exhibited anxiolytic effects in the rat. More recently, a specific AVPR1b antagonist has been developed that shows antidepressant features in rats that parallel the effect of an established antidepressant, fluoxetine hydrochloride. These lines of evidence provide substantial evidence to implicate AVPR1b in the chronic response to stress and in the pathophysiologic mechanism of depression. Furthermore, recent evidence suggests that genetic variation in the AVPR1B gene may be associated with vulnerability to depression.

The gene encoding AVPR1b is located on human chromosome 1q32 and consists of 2 exons that code a 424-amino acid sequence. The AVPR1B receptor is the most homologous with the other vasopressin and oxytocin receptors. Although the genetic region harboring the AVPR1B gene has not been directly implicated in genome scans performed in clinical samples with major depression, it emerged in a genome scan of bipolar disorder, and Nash et al. found a small peak on chromosome 1q in a community-based sample selected on a continuous measure of depression and anxiety. In addition, high-resolution mapping of emotional behavior in mice has found a variety of quantitative trait loci in a region on mouse chromosome 1, which is homologous to the human 1q region.

van West et al. performed mutation screening across AVPR1B in 24 unrelated patients with major depression and identified 5 single nucleotide polymorphisms (SNPs). They proceeded to genotype these markers in 2 small independent samples of patients diagnosed as having major depression and matched controls. Haplotype analysis with the 5 markers identified significant overrepresentation of the same common haplotype in both control samples compared with the subjects. They concluded that this protective haplotype may be a surrogate for a functional DNA change carried on the protective haplotype.

The aim of this study was to investigate the role of the AVPR1B gene in childhood-onset mood disorders (depressive and bipolar disorders) using a large family-based sample from Hungary. Our sample consisted of 382 nuclear families ascertained through a proband with a diagnosis of a mood disorder before the age of 15 years.

**METHODS**

**STUDY PARTICIPANTS**

The sample used in this study is part of a multidisciplinary program project researching multiple risk factors in childhood-onset mood disorders. The Psychiatric Interview Schedule for Children and Adolescents–Diagnostic Version, which is an extension and modification of the Psychiatric Interview Schedule for Children and Adolescents, was used to obtain information for the diagnosis. The proband and the parental informant were interviewed individually on 2 separate occasions approximately 1 month apart by 2 different trained health care professionals. A consensus obtained from 2 other health care professionals trained in best-estimate diagnosis was used as the final diagnosis. The recruitment and assessment of this sample are described in more detail elsewhere.

This study met with institutional review board approval at the University of Pittsburgh, the Centre for Addiction and Mental Health, and all recruitment centers in Hungary. Written informed consent was obtained from each parent and child.

Our sample consisted of 382 families with 464 affected children (382 probands and 82 affected siblings; mean age at first onset, 10.6 years; 6 of the affected siblings’ onset occurred after age 15 years but before age 18 years). The families were re-
Table 1. Primer Sequences and Assay Details

<table>
<thead>
<tr>
<th>SNP</th>
<th>rs No.</th>
<th>Location in Genome (USCS Build 126)</th>
<th>SNP Location</th>
<th>Assay Type</th>
<th>Forward Primer (5’-3’)</th>
<th>Reverse Primer (5’-3’)</th>
<th>Probe Sequence or Extension Primer</th>
<th>PCR Annealing Temperature, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>rs28536160</td>
<td>Chr1:204390006 Chr1:204390006</td>
<td>Promoter region</td>
<td>TaqMan</td>
<td>ACCAGGGCTTCCAGGTCCTAG</td>
<td>AGGGTAGGAGAAAGATGAGGGT</td>
<td>VIC: CTCCTGTCGCCCCCACFAM: CTCCTGTCGCCCCCAC</td>
<td>60.5</td>
</tr>
<tr>
<td>S2</td>
<td>rs28730694</td>
<td>Chr1:204390179 Promoter region</td>
<td>TaqMan</td>
<td>TTTTCTCTTTTCCTATTGCTT</td>
<td>GGCGCTGTGCGGGG</td>
<td>VIC: CTCCTGTCGCCCCCACFAM: CTCCTGTCGCCCCCAC</td>
<td>55.0</td>
<td></td>
</tr>
<tr>
<td>Lyr65Asn</td>
<td>rs3569693</td>
<td>Chr1:204391258 Exon 1</td>
<td>SNaPshot</td>
<td>GACCTCGGCGAGCT</td>
<td>AGGGCATGGAGAACAG</td>
<td>VIC: AGGGCTTGGGCG</td>
<td>59.0</td>
<td></td>
</tr>
<tr>
<td>Arg394His</td>
<td>rs28632197</td>
<td>Chr1:204397581 Exon 2</td>
<td>TaqMan</td>
<td>GCCGCGCCGTACCTT</td>
<td>GAGCGATCTCGGAGG</td>
<td>VIC: AGGGCTTGGGCG</td>
<td>59.0</td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td>rs3985287</td>
<td>Chr1:204397862 3’UTR</td>
<td>SNaPshot</td>
<td>CAGAAAAGAGAAGCTGAGGGG</td>
<td>TCCAGAGTCGAGATTGGG</td>
<td>VIC: AGGGCTTGGGCG</td>
<td>53.0</td>
<td></td>
</tr>
<tr>
<td>S5</td>
<td>rs3933492</td>
<td>Chr1:204397867 3’UTR</td>
<td>SNaPshot</td>
<td>CTGGAAATGAGAGCTGGGAGG</td>
<td>TCCAGAGTCGAGATTGGG</td>
<td>VIC: AGGGCTTGGGCG</td>
<td>53.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Chr, chromosome; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism; USCS, University of California Santa Cruz Genome Browser.

Six SNP markers were genotyped across the AVPR1B gene, 4 of which had been previously identified by van West et al. Unfortunately, we were unable to genotype 1 of the markers (rs33976516) identified in the study by van West et al (named S3) because the assay failed. To determine the reason for the assay failure, the region was sequenced and the genotyping discrepancy was found to be caused by the presence of an SNP at the next base pair. Both S3 and the adjacent SNP have been previously documented by Lida et al (rs33976516 and rs28529127). We further focused our study on 2 non-synonymous SNPs that we identified from a public online database (http://pga.gs.washington.edu). At the time of our study, no information was available in HapMap or dbSNP on this gene, so tag SNPs could not be identified. The 6 SNPs cover 7880 base pairs, and the linkage disequilibrium values for these SNPs in our sample indicate that this gene falls within 1 linkage disequilibrium block (D’ values do not fall below 0.8 for any given marker combination), thus suggesting that this gene has been covered sufficiently in terms of capturing maximum variation.

The single-marker TDT analysis for these 6 markers is given in Table 2. Two SNPs exhibited significant transmission bias of 1 allele to the affected offspring: Lyr65Asn (rs33569693), a nonsynonymous SNP encoding an amino acid change from lysine to asparagine at amino acid 65 (Lys allele T46:NT23: P = .005), and S4 (rs33985287), located in the 3’ untranslated region (A allele T128: NT96: P = .03). Furthermore, a trend was identified with...
SNP S2 (rs28373064), which is located in the promoter region (G allele T93;NT120; $P = .06$). Permutation analysis was performed on the TDT analysis, and the best $P$ value ($P = .005$) still reached statistical significance after 1000 permutations ($P = .02$) (Table 2).

Conditional TDT using UNPHASED was performed to determine if the association obtained for S4 was beyond the indirect association seen through linkage disequilibrium with Lys65Asn. Using Lys65Asn as the conditional marker and S4 as the test marker, the association was no longer statistically significant ($\chi^2 = 1.87, P = .39$), whereas when performing the opposite test, S4 as the conditional marker and Lys65Asn as the test marker, the result remained statistically significant ($\chi^2 = 8.55, P = .01$). These data indicate that the positive association obtained for the SNP S4 can be attributed to the association observed with Lys65Asn.

Haplotype analysis using all 6 markers revealed 1 common haplotype at a frequency of 78% and 2 lower-frequency haplotypes at frequencies of 5% and 6%. Association analysis in our sample found significant overtransmission of the most common haplotype ($P = .001$) and undertransmission of the 5% haplotype ($P = .02$), which reached global significance ($P < .001$) (Table 3).

van West et al22 found their association to be more robust in females than males; because of this, we stratified our sample by sex and examined the transmissions to female and male probands separately using TDTPhase (Table 4). A sex effect was evident in our sample: single-marker analysis for 4 of the SNPs and the haplotype analysis were significant in the females but not in males. This effect cannot be explained by a bias in the number of affected female children because our sample is composed of relatively equal numbers of affected male and female children.

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### Table 2. Transmission Disequilibrium Test Between the AVPR1B SNPs and Childhood-Onset Mood Disorders

<table>
<thead>
<tr>
<th>SNP</th>
<th>Minor Allele Frequency</th>
<th>Transmitted:Not Transmitted (Major Allele)</th>
<th>$\chi^2$ Value</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>T&gt;C</td>
<td>0.07</td>
<td>58:42 (T)</td>
<td>2.57</td>
</tr>
<tr>
<td>S2a</td>
<td>G&gt;A</td>
<td>0.19</td>
<td>93:120 (G)</td>
<td>3.43</td>
</tr>
<tr>
<td>Lys65Asnb</td>
<td>G&gt;C</td>
<td>0.05</td>
<td>46:23 (G)</td>
<td>7.81</td>
</tr>
<tr>
<td>Arg364Hisb</td>
<td>G&gt;A</td>
<td>0.13</td>
<td>84:69 (G)</td>
<td>1.47</td>
</tr>
<tr>
<td>S4b</td>
<td>A&gt;G</td>
<td>0.20</td>
<td>128:96 (A)</td>
<td>4.58</td>
</tr>
<tr>
<td>S5b</td>
<td>G&gt;A</td>
<td>0.13</td>
<td>87:78 (G)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

**Abbreviation:** SNP, single nucleotide polymorphism.

a SNP source: van West et al.22

b SNP source: Seattle SNP database.

c A total of 1000 permutations were performed using UNPHASED on best $P$ value (global significance: $P = .02$; SE = .004).

### Table 3. Transmission Disequilibrium Test Between the AVPR1B 6-Marker Haplotype and Childhood-Onset Mood Disorders Using TRANSMIT

<table>
<thead>
<tr>
<th>Haplotype (S1-S2-Lys65Asn-Arg364His-S4-S5)</th>
<th>Frequency</th>
<th>Observed</th>
<th>Expected</th>
<th>Variance (Observed−Expected)</th>
<th>$\chi^2$ (df=1)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAGGAG</td>
<td>0.78</td>
<td>728.81</td>
<td>703.60</td>
<td>61.96</td>
<td>10.26</td>
<td>.001</td>
</tr>
<tr>
<td>TGAGA</td>
<td>0.05</td>
<td>38.02</td>
<td>48.13</td>
<td>18.44</td>
<td>5.54</td>
<td>.02</td>
</tr>
<tr>
<td>TTGGAG</td>
<td>0.06</td>
<td>66.03</td>
<td>57.67</td>
<td>26.39</td>
<td>2.52</td>
<td>.11</td>
</tr>
</tbody>
</table>

a Global test: $\chi^2 = 42.28, P < .001$. Test on common haplotypes greater than 5%: $\chi^2 = 22.42, P < .001$.

### Table 4. Transmission Disequilibrium Test Analysis of the Sample Stratified by Sex of Affected Offspring

<table>
<thead>
<tr>
<th>SNP</th>
<th>Daughters (n = 214)</th>
<th>Sons (n = 250)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transmitted:Not Transmitted (Major Allele)</td>
<td>$\chi^2$</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** SNP, single nucleotide polymorphism.

a A total of 1000 permutations were performed using UNPHASED on best TDT $P$ value (global significance: $P = .02$, SE = .004).
In this study, we found evidence of an association between genetic markers in the AVPR1B gene and childhood-onset mood disorders. Both single-marker and haplotype analyses produced statistically significant results, even after correction for the use of multiple markers using permutation calculation. Furthermore, the association appears to be sex specific, with the association being restricted to the females in the sample.

The general outcome of this study is supportive of a previous publication. The most common haplotype (78%), however, was associated with affection status, whereas in the previous study the most common haplotype (53%) was protective. This discrepancy could be explained by the divergence of the SNP markers between the 2 studies, which alters haplotypes and their frequencies. For instance, the S3 (rs33976516) marker, which was not typed in this study, appears to split the most common haplotype into 2 haplotypes in the study by van West et al; consequently, the 2 studies are reporting different common haplotypes. It is possible that the common haplotype identified in our study may be refined further with the addition of more markers, splitting the transmitted haplotype into haplotypes biased and nonbiased in transmission.

Computational functional analysis of Lys65Asn using the Web-based protein prediction software program PolyPhen predicted the substitution of the basic amino acid lysine with the acidic amino acid asparagine to be "possibly damaging." Amino acid 65 is located in the first intracellular loop of the protein, and although this change is unlikely to alter AVP binding, it may modify internal cellular signaling through the activation of phospholipase C. A change in this signal transduction system could alter the reactivity of the corticotroph to AVP binding, affecting the release of corticotropin. An additional polymorphism, S4, was also significant in the entire sample and remained so when confining the analysis to females, although conditional TDT analysis indicates that the association found with this SNP is attributable to its high correlation with Lys65Asn. Although these data indicate that the Lys65Asn may be the casual variant responsible for the association seen with other markers, the associated allele is common and thus other factors may be involved, such as additional risk genes and environmental factors. Further investigation is under way to determine the functional relevance of the positive markers and haplotypes.

Sex appears to play an important role in the association of AVPR1B and mood disorders, both in this and the previous study. A recent large twin study that consisted of 15,493 adult twin pairs found that the heritability of depression is greater in females (42%) than males (29%) and that it is probable that at least some of the genetic risk factors are sex specific in nature. In addition, several linkage and association studies in depression have reported sex-specific loci, supporting the existence of sex-dependent genetic effects.

Females are known to be more at risk for developing depressive disorders than their male counterparts, and this increased risk was suggested to be related to the natural fluctuations of estrogen levels during the menstrual cycle. This theory is supported by the observation that the increase in depression in females is not apparent until puberty, when estrogen levels significantly increase. Thus, it is possible that certain genes have genetic variation that could interact with the female endocrine milieu to increase risk of depression.

Despite this apparent role of gonadal hormones in the preponderance of females with depression, it is not clear whether estrogen is the cause of the sex-specific association seen with AVPR1B in this study. Relatively little is known regarding the effects of estrogen on this gene, although the AVPR1B promoter contains an incomplete estrogen response element and a cyclic adenosine monophosphate response element, both of which are present in the CRH gene, which is up-regulated by estrogen. The CRH gene contains 2 half-palindromic estrogen response elements, and even though the elements are not fully intact, they demonstrate weak evidence of estrogenic transcriptional regulation in vivo. Intriguingly, a recent study has suggested a more complicated mechanism of estrogen regulation of CRH via both estrogen receptor β and cyclic adenosine monophosphate response element binding protein. Considering that the AVPR1B promoter contains a cyclic adenosine monophosphate response element binding site and is involved in similar endocrine functions as CRH, AVPR1B could be regulated by estrogen in a similar manner.

One major caveat in focusing on estrogen to explain the observed sex differences seen in this study is that in our sample the mean±SD age of females was 11.3±2.4 years; hence, most girls in our study were prepubescent (the average age for the onset of menarche is approximately 12.5 years; see Parent et al for a recent review). However, evidence has documented an increase in estrogen levels (estrogenization) before the first physical signs of puberty. Furthermore, both the stage of puberty and estrogen levels were found to be more predictive of increased vulnerability to depression in girls than actual age. Therefore, without detailed data on puberty onset and/or estrogen levels for girls in this sample, it is difficult to predict whether the increase in estrogen levels associated with puberty is involved in the sex-specific association seen with this gene. Moreover, because the sex-specific association with AVPR1B has been previously observed in a sample composed of adult women, the sexual immaturity of our sample should not be a major issue. In addition, the effects of estrogen are not confined to a woman’s reproductive years; small levels of estrogen are present in the postnatal, and possibly prenatal, brain that influence brain organization, assisting in the feminization of both the brain and behavior.

An alternative explanation for the sex diathesis may not be directly related to estrogen levels and may be more inherent in brain architecture. Sex differences in vasopressin neuronal projections in the brain have been observed in rats and across divergent vertebrates, suggest-
ing an evolutionary conserved role, although sex differences in AVP brain architecture have not been observed in humans. Nevertheless, sex differences in social communication have been observed with the administration of AVP in humans. Males exhibited agonistic responses to same-sex facial stimuli, whereas females displayed affiliative behavior toward similar stimuli compared with matched controls who were administered saline. These observations are suggestive of a sex-specific effect of AVP; whether this is true of its receptor AVPR1b is not yet clear.

To summarize, we have found evidence that the gene AVPR1b is associated with mood disorders that begin in childhood and adolescence. In particular, we found an association with a potentially functional SNP that could influence internal cellular signal transduction. Further work should seek to replicate these findings, investigate the mechanisms behind the apparent sex-specific effect, and examine the functional implications of the polymorphisms associated with mood disorders in this sample.

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density genome scan detects evidence for a bipolar-disorder susceptibility loci on 13q32 and other potential loci on 1q32 and 18p11.2. Proc Natl Acad Sci U S A. 1999;96(10):5604-5609.


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