Published in final edited form as:
Psychiatry Res. 2012 May 15; 197(1-2): 49–54. doi:10.1016/j.psychres.2011.11.022.

Association Study of Early-Immediate Genes in Childhood-Onset Mood Disorders and Suicide Attempt

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Keywords

early-immediate gene; pediatric; mood disorder; suicide attempt

1. Introduction

Growing evidence from basic and clinical experiments support a hypothesis that stress and depression are associated with alterations in hippocampal neurogenesis and neurotrophic factor expression, and that antidepressant treatment reverses or blocks such results (Schmidt and Duman, 2010; Schmidt and Duman, 2007; Duman et al., 1997). BDNF is a prototypical neurotrophic factor (Castren 2005; Lee et al., 2001; Levine et al., 1995). The preclinical literature on BDNF in stress-related depression has been supported by multiple published human studies on BDNF as a putative biomarker for mood disorder phenotypes (e.g. Shimizu et al., 2003; Cunha et al., 2006; Machado-Vieira et al., 2007; Monteleone et al., 2008). BDNF and its receptors have been implicated in suicidal behaviour (Dwivedi et al., 2003; Karege et al., 2005; Ernst et al., 2009; Kunugi et al., 2004; Kim et al., 2007). Several genetic studies have implicated *BDNF* and neurotrophin receptor gene polymorphisms in pediatric mood disorder phenotypes (Geller et al., 2004; Strauss et al., 2004, 2005; Kaufman et al., 2006; Hilt et al., 2007; Wichers et al., 2008; Feng et al., 2008).

Childhood-onset mood disorders (COMD) are pernicious affective illnesses, which can take the form of major depressive disorder (MDD), dysthymic disorder (DD) or bipolar disorder (BP). COMD impede normal development and heighten the risk for morbidity - including substance abuse and SA and completed suicide (Birmaher et al., 1996). There is substantial evidence that COMD increases risk for SA and suicide (Sanchez and Le, 2001). Variation in depressive symptoms in juvenile populations is under significant hereditary influence (Boomsma et al., 2005; Hudziak et al., 2000; Rice et al., 2002), evidence that supports molecular genetic approaches.

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Our aim was to test for association between markers at other neuroplasticity genes and COMD, and between those markers and SA. Since BDNF was identified as a neuroplasticity-related compound by its antidepressant-like effects in animal models (Schmidt and Duman, 2007; Duman et al., 1997), our candidate gene selection was based on similar animal and human paradigms, including electroconvulsive seizures (ECS) (Bocchio-Chiavetto et al., 2006; Grønli et al., 2007; Marano et al., 2007) and exercise (Ferris et al., 2007). Candidate genes selected: 1) were significantly altered (in parallel to BDNF) by electroconvulsive seizures (ECS) and/or exercise, 2) are related to BDNF by being in the same biochemical pathway; or 3) influence neurogenesis. Based on preclinical gene expression studies outlined below, we chose *HOMER1* and human neuronal pentraxin II (*NPTX2*). Furthermore, both are early-immediate genes (EIGs).

Like Bdnf, Homer1 is upregulated by ECS in the frontal cortex and hippocampus (Altar et al., 2004) and is also upregulated by exercise in the hippocampus (Tong et al., 2001). Chronic stress downregulates Homer1 expression in rat prefrontal cortex; the effect is reversed with antidepressant administration (Orsetti et al., 2008, 2009). Homer1 has EIG and constitutive effects that influence synapses (Xiao et al., 1998; Ango et al., 2002). *Homer1* knockout (KO) mice show decreased sensory responsiveness, motor function, activity cycles, and learning (Jaubert et al., 2007), in addition to enhanced 'behavioral despair', increased anxiety in a novel objects test, and decreased instrumental responding to sucrose (Szumlinski et al., 2005), changes similar to those observed in animal stress paradigms (Schmidt and Duman, 2007). Over-expression of Homer1 protein induces symptomatic recovery of *Homer1* KO mice (Lominac et al. 2005). The animal evidence suggests a possible role for *HOMER1* in human depressive symptoms. A handful of human genetic association studies are point to relevance of HOMER1 in human psychopathology. For example, two putative functional *HOMER1* SNPs have recently been associated with major depressive disorder in a genome-wide association study (GWAS) and imaging study -- rs7713917 was associated with prefrontal cortical activity during executive function (Rietschel et al., 2010). Additionally, *HOMER1* rs4704560 has been implicated as a possible susceptibility variant for psychotic symptoms in Parkinson's disease (De Luca et al., 2009). Furthermore *HOMER1* rs2290639 and rs4704560 have been associated with baseline psychopathology and multiple *HOMER1* SNPs have been associated with therapeutic response in schizophrenia (Spellman et al. 2011).

NPTX2 is an EIG from the pentraxin family (Hsu and Perin, 1995; Reti and Baraban, 2000; O'Brien et al., 1999), located on chromosome 7q21.3-22.1, (Hsu and Perin, 1995), a genomic region that has been implicated in linkage studies of bipolar disorder (Segurado et al., 2003; Cheng et al., 2006). Frontal cortical and hippocampal expression of the *NPTX2* rat homolog (*Narp*) are elevated following ECS (Tsui et al., 1996; Reti and Baraban, 2000; Altar et al., 2004); hippocampal *Narp* levels increase following exercise (Tong et al., 2001). Narp is upregulated following BDNF long-term potentiation (LTP) in the rat dentate gyrus (Wibrand et al., 2006). Animal studies illustrate a potential role for *NPTX2* in synaptic plasticity, and a positional candidate for human mood disorders via linkage studies of bipolar disorder.

The current study was undertaken in order to examine if *HOMER1 or NPTX2* gene variants are associated with COMD or SA. We hypothesized that SNPs at both candidate EIGs would be associated with COMD or SA.

2. Methods

2.1 Subjects

COMD participants were recruited as part of the Risk Factors in Childhood-Onset Depression Program Project at the University of Pittsburgh. These subjects have been described previously (Strauss et al., 2004; McGregor et al., 2007). The current study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and with the approval of the institutional review board at the Centre for Addiction and Mental health (CAMH) in Toronto and at the University of Pittsburgh Medical Center. Written informed consent was obtained for all participants. Some of the participants that were recruited from previous studies on childhood mood disorders had extensive research records supporting the required diagnosis and were interviewed using a young adult version of a clinical interview – the ISCA (Sherrill and Kovacs, 2000). The other clients that were recruited via mental health clinics and community advertisements were assessed using a modified version of the Structured Clinical Interview for DSM-IV Axis I disorders, Patient Edition (SCID) (First et al., 1995), and were required to have childhood medical or psychosocial records supporting pediatric onset of mood disorder. Interviews were conducted by professional-level clinical evaluators. All clients were diagnosed using DSM-III (American Psychiatric Association 1980) or DSM-IV TR (American Psychiatric Association 2000) for major depressive disorder (MDD) or dysthymic disorder (DD) with onset by 13.99 years of age, or bipolar (BP) I or II disorders with onset by 16.99 years of age, using best estimate consensus diagnosis (Maziade et al., 1992). Venous blood was collected (15mL) from each client at the University of Pittsburgh Medical Center and preserved in EDTA. The samples were then couriered to CAMH in Toronto, Canada where DNA was extracted and genotyped. The sample consisted of a total of 201 COMD probands, with 105 having a history of at least one life-time SA and the other 96 clients had no SA at the time of the current study. The ISCA defines SA as an executed or completed behavior that could potentially result in death of the individual, or the belief that it could; the SA behavior must be volitional and self-induced with some psychological intent to cause death to oneself. For the COMD versus control comparisons, 191 of the 201 probands were able to be matched for sex and ethnicity to healthy controls making a total of 382 individuals for these comparisons (191 cases; 191 matched controls); these healthy controls have been described previously (Strauss et al., 2004; McGregor et al., 2007). Our controls had no history of psychological disorder based on screening questions from the SCID interview and were healthy adults. They were ascertained from surgical clinics, undergraduate university students, and newspaper advertisements, both in Toronto and through research collaborators.

2.2 Laboratory

The extraction of DNA used a high salt method (Lahiri and Nurnberger, 1991). Individuals were genotyped at a total of ten SNPs: *HOMER1* rs7713917, rs4704560, rs2290639, rs2404150, rs770276, rs4132033, rs10942889; and *NPTX2* rs1681248, rs705318, rs705315. SNPs were selected based on a reported minor allele frequency of >0.20 and assay availability at the time, as well as the more recent addition of *HOMER1* rs7713917 (Rietschel et al., 2010) and rs4704560 (De Luca et al., 2009; Spellman et al., 2011). We used standard ABI TaqMan® assay-on-demand allelic discrimination amplification assays at a10μL volume. For all PCR reactions, a protocol of 50ng genomic DNA was denatured for 10 min. at 95°C and amplified over 50 cycles of 15 sec. at 92°C and 1 min. at 60°C in an MJ Research thermocycler (Bio-Rad Laboratories, Hercules, CA). Post-amplification products were quantified on the ABI PRISM® 7300 and 7500 Sequence Detection System (Applied Biosystems, Inc., Foster City, CA). Genotypes were manually assigned.

2.3 Statistical methods

Genotype frequencies were compared between COMD cases and controls using chi-square methods, and Fisher's exact test where appropriate, using R (http://www.r-project.org/). Haploview v4.1 (Barrett et al., 2005) was used to examine genotype completion rates, Hardy-Weinberg equilibrium, linkage disequilibrium (using the Solid Spine algorithm) and allele and haplotype association.

To correct for testing multiple SNPs, spectral decomposition methods (Nyholt 2004) were used to adjust alphas for both *HOMER1* and *NPTX2* – the experiment-wide significance thresholds required to keep the Type I error rate at 5% were 0.0102 for *HOMER1* and 0.0226 for *NPTX2*, respectively (Li and Ji, 2005).

Gene-gene interaction was calculated using multifactor dimensionality reduction (MDR) (Hahn et al. 2003; Moore 2004). The best model was selected based on Testing Balance Accuracy (TBA). Significance of interaction was calculated by permutation as implemented in MDR-permutation testing. *HOMER1* rs7713917 had a degree of missingness that created unbalanced groups and therefore MDR analyses excluded rs7713917.

3. Results

Genotypes were >= 97.6% complete for the COMD analyses (with the exception of rs7713917 at 93.5%), and >= 99% for the SA analyses. Most markers across both COMD and SA analyses were in HWE (p-values >0.0537), with the exception of three SNPs at *HOMER1* – rs2290639(p=0.0063), rs2404150(p=0.0016) and rs4704150(p=0.0098). However, within European American (EA) and African American (AA) subgroups HWE was observed for these *HOMER1* SNPs.

Considering COMD probands only, when comparing 105 attempters (SA+) and 96 non-attempters (SA−), there were no significant differences in ethnicity or in diagnostic polarity. Lifetime history of SA was more common in females (chisq=4.39, d.f.=1, p=0.04) and those with alcohol abuse (chisq=5.10, d.f.=1, p=0.02) (Table 1). There were no significant differences in genotype frequencies between COMD cases and matched controls (Table 2). Concerning allelic association, the *HOMER1* rs7713917 SNP was nominally associated with COMD at p=0.04.

Genotype analyses of COMD with a history of lifetime SA (SA+) versus COMD with no lifetime SA (SA−) are presented in Table 3. The *HOMER1* rs2290639 SNP was statistically significant with SA+ individuals having more TT homozygotes and fewer heterozygotes than SA− (Chisq= 12.42, df = 2, p = 0.003). Another *HOMER1* SNP rs2404150, was nominally associated with SA (p = 0.04). *NPTX2* rs705315 was significantly associated with SA+ individuals having a greater frequency of the GG genotype (Fisher's Exact Test, p = 0.01). *NPTX2* rs1681248 showed a significantly higher frequency of the GG genotype (Fisher's Exact Test, p = 0.006). Allelic comparisons (not shown) demonstrated nominally significant association between *NPTX2* rs1681248 G allele and SA (chisq=5.29, p=0.021), and trends towards association for the other two *NPTX2* SNPs-- rs705318 (p=0.054) and rs705315 (p=0.07). There were no other differences in SNP allele frequencies between SA+ and SA−.

HOMER1 and *NPTX2* linkage disequilibrium measures are reported in Supplementary Tables and Figures for both COMD and SA analyses. The results are quite similar between COMD and SA, so COMD will be summarized. *HOMER1* had three blocks – Block 1 (containing rs2290639, rs2404150 and rs7702760), Block 2 (rs4132033 and rs10942899) and Block 3 (rs4704560 and rs7713917). Distances between the closest markers were at

least 14kb. Within-block D-prime values were all at least 0.82, with r^2 results >= 0.31. *NPTX2* had a single block with D-prime values >= 0.845, and r^2 >= 0.165, all three markers were within 5kb.

There were no haplotypes associated with COMD Two nominally significant haplotype associations were observed with SA (a *HOMER1* G-G haplotype (p=0.032); a NPTX2 C-T-A haplotype (p=0.029)) (see Supplementary Tables and Figures). MDR was also performed on the suicide phenotype. Significant three-locus synergistic interaction was observed among two SNPs in *HOMER1* - rs4704560, rs2290639, and a SNP in *NPTX2* - rs705318 (TBA=0.6565, p=0.015). Among the two locus interactions, the top model included a SNP rs2290639 in *HOMER1* and rs1681248 in *NPTX2* (TBA=0.631, p=0.036). However, the interaction appears to be redundant or correlated and no new information is gained.

4. Discussion

The current study found no association between any EIG markers and COMD, by genotype, haplotype or allele. Within COMD cases, we noted an association between SA and *HOMER1* rs2290639 genotype, as well as between SA and *NPTX2* rs705315 and rs1681248 genotypes – results that remained significant after correcting for multiple tests. Heterozygotes for rs2290639 or rs705315 had fewer SAs than homozygous participants, which suggest possible heterozygote advantage. Additionally we report nominally significant haplotype associations with SA at both *HOMER1* and *NPTX2.* We also described MDR results suggestive of possible two- and three-way interactions between HOMER1 and NPTX2 (p-values=0.036, 0.015).

As outlined above, previous human and animal studies have implicated *HOMER1* in mental disorders, including depression. While the literature suggests *HOMER1* may be germane to COMD, our results do not support an association after adjusting our signficance threshold for multiple tests. This may be because we are examining a different phenotype than prior studies, or possibly because of the modest sample size. Indeed, our relatively underpowered sample yielded nominally significant allelic association between the HOMER1 rs7713917 SNP (Rietschel et al. 2010) and COMD at p=0.04, a result that did not survive multiple testing correction. We describe an association between *HOMER1* rs2290639 genotype and SA in COMD. To our understanding, previous investigations of *HOMER1* have not reported on either of the specific phenotypes we examined – mood disorders with pediatric onset, and suicide attempt. Rietschel and colleagues (2010) work is notable, among many things, for the association of rs7713917 with MDD and prefrontal cortical activity, as this SNP is in the same block as the transcription start site and 70% of *HOMER1* transcription factor binding sites (Rietschel et al. 2010). Our nominally significant MDR gene interaction finding involving rs4704560 may be relevant as rs4704560 is a putative promoter polymorphism close to the transcription start site (De Luca et al. 2009), and rs4704560 is in the same block as rs7713917; the variants are in high linkage disequilibrium. Moreover, Spellman et al.'s (2011) findings are relevant to mood disorders as the PANSS negative symptoms score were associated with rs4704560 in their sample – and the PANSS-N is used to measure depression in schizophrenia patients and is also correlated with the Hamilton Depression Rating Scale (Kontaxakis et al., 2000).

Although *NPTX2* has been studied in autism (Marui et al., 2007), we know of no prior association studies of *NPTX2* in MDD or SA. COMD probands with a history of SA had a lower frequency of heterozygotes at the marker rs705315 and rs1681248. As described in the introduction, neuroplasticity appears to be an important mechanism in both mood and SA, and it is possible that NPTX2 is involved in SA through this mechanism.

Any possible biological significance of our findings at this time would be speculative. Nonetheless, our findings are of germane in relation to the role of BDNF in suicide, and the direct effect of BDNF on neuronal signalling and Homer1 expression (Ji et al., 2010). The nominally interactions we describe highlight the importance of biological pathway network analyses in genome-scale studies.

Limitations of our investigation should be acknowledged. Multiple testing and the associated increase in risk of false positives are relevant to our results. Because of this, we corrected for multiple SNPs tested using SNPSpD, (Nyholt, 2004). Further, our sample power is modest -- our 201 matched case-control pairs provide 86% power to detect a genotype relative risk as low as 1.8, and very conservatively, a power of 0.56 to detect a GRR of 1.4; given the assumptions of alpha = 0.05, population frequency of 2%, additive model of inheritance, minor allele frequency of 0.45 (minor allele frequency for *HOMER1* rs2290639= 0.45), a general 2 d.f. Test, and complete linkage between risk and disease variants (Purcell et al., 2003). A larger sample size would be beneficial to strengthen our results. Also, population stratification must be considered. Though not statistically significant, SAs are more frequent in African-Americans than in European Americans in our study. Since rs2290639 is monomorphic for the A allele in HapMap YRI (African) sample but not in the CEU (European) sample, it suggests the possibility that the reduced risk for SA we observed with rs2290639 heterozygotes may be related to European American ancestry. In contrast, rs705315 is more heterozygous in HapMap YRI than CEU, suggesting that the reduced risk for rs705315 heterozygotes is not related to European American ancestry. Although population substructure may contribute to our results, our previous use of genomic controls in a subset of this sample indicated no evidence of stratification (Strauss et al., 2004). Lastly, another significant limitation is that the SNP selection and related coverage of the large *HOMER1* region is far from exhaustive. In summary, we report associations between *HOMER1* rs2290639 genotype and SA, as well as between *NPTX2* rs705315 genotype and SA, as well as nominally significant allelic association between rs7713917 and COMD, and nominally significant gene-gene interactions by MDR, interactions involving HOMER1 rs2290639 and rs4704560. Future experiments should consider larger samples, denser mapping of the region, and including more putative functional polymorphisms. In support Rietschel et al. (2010), we find weak evidence of a main effect of *HOMER1 rs7713917* in COMD. Notably, their findings were in adult MDD samples and may not apply to our COMD participants with documented pediatric onset of depressive disorder. We do note associations of SNPs from *HOMER1* and another EIG, *NPTX2,* with the SA phenotype. Overall, given the strong biological rationale for a role for HOMER1 and NPTX2 in animal paradigms, and evidence from human genetic studies, future investigations may yield salient findings of considerable interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the American Foundation for Suicide Prevention Young Investigator Grant (JS) and by the NIMH Program Project # P01 MH056193 (JLK, MK).

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Table 1

Demographics and Clinical Characteristics

		SA+	SA−	Chi-square	P	d.f.
Ethnicity	AA	24	14	1.73	0.18	1
	EA	81	82			
Gender	Male	28	40	4.39	0.04	1
	Female	77	56			
Diagnosis	Unipolar	62	67	2.07	0.15	1
	Bipolar	43	29			
LTETOH	Yes	56	35	5.1	0.02	1
	No	49	61			

SA+ – lifetime history of at least one lifetime suicide attempt

SA− – lifetime history negative for suicide attempt

AA – African American

EA – European American

LTETOH – lifetime history of alcohol abuse

Psychiatry Res. Author manuscript; available in PMC 2013 May 15.

Table 2

Childhood Onset Mood Disorders (COMD, n=191) versus healthy controls (HC, n=191): Genotype distributions for *HMR1* and *NPTX2* polymorphisms

Locus	SNP	Phenotype	Genotype			Chisq	Genotype p	d.f.	Allele p
HOMER1	rs7713917		AA	AG	GG				
		COMD	41	86	61	4.12	0.13	2	0.04
		HC	24	78	67				
	rs4704560		CC	CT	TT				
		COMD	50	84	55	1.69	0.43	2	0.20
		HC	43	76	65				
	rs2290639		TT	TA	AA				
		COMD	45	92	55	4.35	0.11	2	0.82
		HC	53	71	66				
	rs2404150		GG	GA	AA				
		COMD	38	80	74	0.65	0.72	2	0.52
		HC	44	75	71				
	rs7702760		CC	CA	AA				
		COMD	18	72	102	1.81	0.40	2	0.57
		HC	15	84	91				
	rs4132033		GG	GC	CC				
		COMD	56	92	44	0.08	0.96	2	0.78
		HC	53	92	45				
	rs10942889		TT	TG	GG				
		COMD	54	86	52	1.17	0.55	2	0.56
		HC	45	94	51				
NPTX2	rs1681248		GG	GC	CC				
		COMD	157	31	3	FET	0.97	-	0.86
		HC	154	32	3				
	rs705318		TT	TG	GG				
		COMD	32	77	83	2.98	0.23	2	0.97
		HC	24	92	74				
	rs705315		GG	GA	AA				

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Locus	SNP	Phenotype	Genotype			Chisq	Genotype p	d.f.	Allele p
		COMD	160	28	4	FET	0.77	-	0.77
		HC	155	32	3				

FET, Fisher's Exact Test;

COMD: Childhood-Onset Mood Disorder, n = 191

HC: Healthy Controls, n=191

Table 3

COMD attempters (n=105) versus non-attempters (n=96): Genotype distributions for *HOMER1* and *NPTX2* polymorphisms

Locus	SNP	Phenotype	Genotype			Chisq	Genotype p	d.f.	Allele p
HOMER1	rs7713917		AA	AG	GG				
		SA+	21	49	35	0.15	0.93	2	0.70
		SA−	21	44	30				
	rs4704560		CC	CT	TT				
		SA+	27	50	28	0.76	0.68	2	0.67
		SA−	25	40	30				
	rs2290639		TT	TA	AA				
		SA+	30	39	36	12.42	0.003 *	2	0.64
		SA−	14	58	24				
	rs2404150		GG	GA	AA				
		SA+	26	40	39	6.27	0.04	2	0.11
		SA−	11	47	38				
	rs7702760		CC	CA	AA				
		SA+	10	44	51	2.84	0.24	2	0.11
		SA−	7	31	58				
	rs4132033		GG	GC	CC				
		SA+	25	51	29	3.31	0.19	2	0.07
		SA−	33	44	19				
	rs10942889		TT	TG	GG				
		SA+	27	44	34	2.79	0.25	2	0.13
		SA−	29	46	21				
NPTX2	rs1681248		GG	GC	CC				
		SA+	93	10	2	FET	0.006 *	-	0.02
		SA−	71	24	1				
	rs705318		TT	TG	GG				
		SA+	14	40	51	5.84	0.05	2	0.05
		SA−	20	40	36				
	rs705315		GG	GA	AA				

Locus	SNP	Phenotype	Genotype			Chisq	Genotype p	d.f.	Allele p
		SA+	93	9	3	FET	0.01*	-	0.07
		SA−	73	22	1				

FET: Fisher's Exact Test

COMD: Childhood-Onset Mood Disorder

SA+: COMD with history of lifetime suicide attempt, n = 119

SA−: COMD with no history of lifetime suicide attempt, n = 109

*Significant after spectral decomposition (SNPSpD; Nyholt, 2004)