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Variation in SWI/SNF chromatin remodeling complex proteins is associated with alcohol dependence and antisocial behavior in human populations

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Abstract

Background—Testing for direct gene/SNP replication of association across studies may not capture the true importance of a candidate locus; rather, we suggest that relevant replication across studies may be found at the level of a biological process. We previously observed that variation in two members of the SWI/SNF chromatin remodeling complex is associated with alcohol dependence (AD) in the Irish Affected Sib Pair Study for Alcohol Dependence. Here, we tested for association with alcohol-related outcomes using a set of genes functioning in the SWI/SNF complex in two independent samples.

Methods—We used a set-based analysis to examine the 29 genes of the SWI/SNF complex for evidence of association with (1) AD in the adult Collaborative Study on the Genetics of Alcoholism (COGA) case/control sample and (2) antisocial behavior, hypothesized to be a genetically-related developmental precursor, in a younger population sample (Spit for Science).

Results—We found evidence for association of the SWI/SNF complex with AD in COGA ($p=0.0435$) and more general antisocial behavior in Spit for Science ($p=0.00026$). The genes that contributed most strongly to the signal in COGA were *SSI8L1*, *SMARCD1*, *BRD7*, *SMARCB1* and *BCL11A*. In the Spit for Science sample, *ACTB*, *ARID2*, *BCL11A*, *BCL11B*, *BCL7B*, *BCL7C*, *DPF2*, and *DPF3* all contributed strongly to the signal.

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Conclusions—We detected associations between the SWI/SNF complex and AD in an adult population selected from treatment-seeking probands and antisocial behavior in an adolescent population sample. This provides strong support for a role for SWI/SNF in the development of alcohol-related problems.

Keywords

Alcohol Dependence; SWI/SNF; COGA; chromatin remodeling; externalizing; antisocial behavior

Introduction

Alcohol dependence (AD) is a significant social and economic problem. The propensity to develop AD is strongly influenced by genetics (Rodriguez et al., 1993, Heath et al., 1999, Schuckit and Smith, 1996, Prescott and Kendler, 1999, Schuckit, 2000), but few of the specific genetic factors underlying this propensity have been identified. One major problem with the identification of strong candidate genes in humans is that promising signals are frequently not replicated across studies at the level of the individual polymorphism or gene. Because variation in different genes that act together in a biological process may yield similar phenotypic outcomes, we suggest that identification of associated variation in different genes controlling the same process across studies strongly supports a role for that biological process in AD. For this reason, biological process-based set analyses may provide more reliable and replicable results than individual gene-specific analyses. Here, we assess the association of all genes known to act together to perform a common biological action with alcohol-related outcomes in an adult sample drawn from six treatment centers, the Collaborative Study on the Genetics of Alcoholism (COGA) study, and in a younger population sample, the Spit for Science (S4S) sample, to determine the importance of a protein complex in AD liability.

SWI/SNF (SWItching defective/Sucrose Non-Fermenting) is a multi-protein complex that regulates chromatin structure by altering the associations between DNA and histones, which can lead to changes in gene expression. Chromatin remodeling is one mechanism of epigenetic gene regulation (Allis and Jenuwein, 2016), and members of the SWI/SNF chromatin remodeling complex have been implicated as epigenetic regulators in the development of cancer (Kadoch and Crabtree, 2015, Nickerson et al., 2017). The complexes contain an enzymatic core of four subunits and several accessory subunits that vary with distinct SWI/SNF complex types (Fig. 1; Son and Crabtree, 2014). Different accessory subunits lend specificity to the function of the different complexes; some accessory subunits are found in all complexes, while others are specific to a particular type of SWI/SNF complex (Kadoch and Crabtree, 2015, Son and Crabtree, 2014).

Two major families of SWI/SNF complexes are BAF (Brg1-Associated Factors) and PBAF (Polybromo-associated BAF), which incorporate different sets of unique accessory subunits to produce molecularly distinct complexes (Fig. 1A). We previously found that BAF and PBAF affect different components of the acute response to ethanol in the genetic model *Caenorhabditis elegans* (Mathies et al., 2015): BAF is required for normal initial sensitivity to ethanol, while PBAF is required for the development of acute functional tolerance to

ethanol (AFT). We found that PBAF functions in differentiated neurons for the development of AFT (Mathies et al., 2015). Importantly, variation in two human SWI/SNF complex genes, *SMARCA2* and *BRD7*, was associated with AD in the Irish Affected Sib Pair Study for Alcohol Dependence (IASPSAD) (Mathies et al., 2015).

In the current study, we had the goal of expanding this literature in two ways: (1) by testing whether genes involved in the SWI/SNF complex were associated with AD in a second independent human adult sample, similarly ascertained through probands in treatment centers, like the IASPSAD sample; and (2) by testing whether the complex influenced developmental precursors of alcohol-related outcomes in a younger adolescent sample. A large portion of the genetic predisposition to alcohol dependence has been shown to be via a general predisposition toward externalizing behavior (Kendler et al., 2003, Krueger et al., 2002, Dick et al., 2005, Slutske et al., 1998), that manifests as different phenotypes at different developmental stages (Dick et al., 2006). It has been robustly demonstrated that conduct problems in children and adolescents are associated with the subsequent development of AD (Molina et al., 2002, Kuperman et al., 2001) and, importantly, that childhood conduct problems are genetically related to adult AD (Trucco et al., 2016, Kendler et al., 2003, Slutske et al., 1998). Several genes that have been associated with adult AD have been shown to influence behavior problems in younger adolescents before the onset of alcohol problems, suggesting that behavior problems in younger individuals are an earlier phenotypic manifestation of a genetic predisposition that subsequently influences alcohol problems in adults (Dick et al., 2013, Dick et al., 2016). Accordingly, we hypothesized that in our younger population sample of adolescents, the SWI/SNF gene set may impact antisocial behavior rather than alcohol dependence *per se*.

In this study, we examined all 29 genes encoding known subunits of the SWI/SNF chromatin remodeling complex in humans for association with AD in the COGA adult case-control sample (Bierut et al., 2002) and with antisocial behavior in the younger S4S sample (Dick et al., 2014). We further hypothesized that we would find evidence for replication of association of SWI/SNF genes at the level of the biological complex, rather than at the level of individual SNPs or genes, which may vary from sample to sample.

Materials and Methods

COGA case-control sample

Sample—The Collaborative Study on the Genetics of Alcoholism (COGA) is a multi-site project, with the goal of identifying genes contributing to alcoholism and related phenotypes. Probands were identified through inpatient or outpatient alcohol treatment programs at six sites around the United States and were invited to participate if they had a sufficiently large family (usually sibships > 3, with parents available) with two or more members living in a COGA catchment area (Begleiter et al., 1995). The institutional review boards of all participating centers approved the study. Written consent was obtained from all study participants. Additional details about the study have been published previously (Foroud et al., 2000, Edenberg et al., 2004, Reich et al., 1998). The sample has $n=1905$ individuals (1205 cases and 700 controls). The sample is 46% female; 74% of the sample self-identified as European American, and 26% as African American.

Genotyping—For COGA case control samples, genotyping was performed by the Center for Inherited Disease Research (CIDR). DNA sources included blood ($n=1453$) and lymphoblastoid cell lines (LCL, $n=492$). Genotyping was performed using the Illumina Infinium II assay protocol (Gunderson et al., 2006) with hybridization to Illumina HumanHap1M BeadChips (Illumina, San Diego, CA, USA), which contain 1,199,187 markers with a mean spacing of 2.4 kb. Allele cluster definitions for each SNP were determined using Illumina BeadStudio Genotyping Module version 3.1.14 and the combined intensity data from 96% of study samples. The resulting cluster definition file was used on all study samples to determine genotype calls and quality scores. Genotype calls were made when a genotype yielded a quality score (Gencall value) of 0.15 or higher. The final raw dataset with 1,041,465 SNPs for 1,945 unique DNA samples from case and control subjects was imputed to 1000G platform phase 3, b37, October 2014 and filtered based on info criterion <0.3 , genotyping rate <0.9 , MAF <0.005 and HWE $<10^{-6}$.

Phenotype—Assessment was based on the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994). DSM-IV alcohol dependence was defined by the clustering of 3 or more dependence criteria in a 12-month period.

Analyses—We used the program PLINK (Purcell et al., 2007, Chang et al., 2015) to run set-based analyses for alcohol dependence diagnosis. The p -value threshold used in set-based analyses was 0.01, and the r^2 threshold for LD pruning was set to 0.5. Gender and two race principal components were used as covariates.

S4S sample

Sample—Spit for Science (S4S) is a longitudinal study of college students enrolled in a large, urban university in the Mid-Atlantic region of the United States, as previously described (Dick et al., 2014). Briefly, all incoming students age 18 or older were invited to complete surveys with content related to alcohol use and related behavioral and emotional health outcomes in the fall of their first semester. Study data were collected and managed using REDCap electronic data capture tools (Harris et al., 2009). Participants who completed the phenotypic assessments were eligible to provide a DNA sample. The current study includes three cohorts, which matriculated in fall 2011 ($n = 2,714$), 2012 ($n = 2,486$), and 2013 ($n = 2,403$), for a total $n = 7,603$. Of these, 98% provided a DNA sample. The average ($\pm$ SD) age was 18.59 (± 0.61), and 61% of the sample was female. Self-report race/ethnicity for the sample was 15% Asian, 20% African American, 7% Hispanic, 6% more than 1 race, and 50% White, which closely maps onto overall university demographics (Dick et al., 2014).

Genotyping, Pre-imputation QC, and Imputation—There were 6534 samples passing DNA and initial genotyping quality control (QC). Genotyping was performed at Rutgers University Cell and DNA Repository (RUCDR) using the Affymetrix BioBank array (653K variants) which contains both common GWAS framework variants (296K) for imputation and functional variants (357K) including rare high impact exome variants (272K), indels (18K), eQTLs (16K), and miscellaneous variants (51K). QC excluded Off Target Variants found by SNPfilter, single nucleotide polymorphisms (SNPs) missing $>5\%$ of genotypes,

samples missing >2% of genotypes, and SNPs missing >2% of genotypes after sample filtering, similar to the Psychiatric Genomics Consortium (PGC; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). This pre-imputation QC removed 209 samples, leaving 6,325 samples and 560,138 variants for imputation. Imputation was conducted using SHAPEIT2 (Delaneau et al., 2013), IMPUTE2 (Howie et al., 2009) and the 1000 genomes phase 3 reference panel ($n = 2,504$) (Sudmant et al., 2015, 1000 Genomes Project Consortium et al., 2015).

Phenotype—Antisocial behavior was assessed in the fall surveys via a six-item scale in which individuals retrospectively reported on behavior during the high school period. The score was created as a standardized sum of six responses (I skipped school, I ran away from home overnight, I stole things from a store or from someone I knew, I used a weapon in a fight, I robbed or mugged someone, I started physical fights) with four response options (3=6 or more times, 2=3–5 times, 1=1–2 times, 0=never). Missing data was prorated. Individuals not answering 50% of questions were assigned as missing.

Analyses—We used the program PLINK to run set-based analyses for the antisocial behavior phenotype using the same options as in the COGA sample. Race, cohort, gender and six non-collinear race principal components were used as covariates.

Results

COGA case/control sample

We began by testing if the entire set of 29 genes encoding members of the SWI/SNF complex was associated as a whole with a phenotype of AD in the COGA case/control sample. We found that, using a set-based analysis, the 29 genes in the SWI/SNF complex was associated with alcohol dependence at $p=0.0435$. We next asked which of the genes in the set of 29 contributed to this association by performing individual gene-based tests on each gene. Table 1 shows the results for individual gene-based tests. We found that *SS18L1*, *SMARCD1*, *BRD7*, *SMARCB1* and *BCL11A* were all significant at $p<0.05$.

S4S Sample

The Spit for Science sample members are young, and therefore appropriate for examining the genetic contributions to an antisocial behavior phenotype that has been described as an early predictor of alcohol problems (Kuperman et al., 2001, Kessler et al., 1997, Zucker, 2008). We tested if there was an association between SWI/SNF complex members and antisocial behavior. We began by testing the set of 29 known SWI/SNF genes as a whole, and found that the set-based analysis of the SWI/SNF complex genes showed significant association with antisocial behavior in the Spit for Science sample ($p=0.00026$). We next used gene-based analyses to identify the members of the set that were contributing to this signal. We found that *ACTB*, *ARID2*, *BCL11A*, *BCL11B*, *BCL7B*, *BCL7C*, *DPF2*, and *DPF3* all yielded $p<0.05$, contributing to the highly significant association of the set (Table 2).

Discussion

The propensity to develop AD is strongly influenced by genetics (Rodriguez et al., 1993, Heath et al., 1999, Schuckit and Smith, 1996, Prescott and Kendler, 1999, Schuckit, 2000), and human genetic association studies have identified a variety of candidate loci that are associated with the propensity to develop AD in individual populations (Tawa et al., 2016, Hart and Kranzler, 2015). However, very few of these associations, excepting loci in the *ADH* and *ALDH* genes, have been replicated across different studies. One possible reason for the difficulty that has been observed in replicating associations for AD is that traditional replication analysis, in which the same allele or gene is examined in more than one study, presupposes that identical or equivalent mutational events in a given gene must occur across populations to cause the phenotype. This stringent requirement may not appropriately capture the potential role of the gene in AD because it fails to take into account how broader gene networks function. Because genes act together in biological networks to perform a particular function, we reasoned that if a biological process is important in modulating the propensity to develop AD, then variation in any genes similarly affecting that process might cause a similar change in the liability to develop AD. We therefore tested all members of the SWI/SNF chromatin remodeling complex *as a set* to evaluate association with AD and a related phenotype in two human samples because we had evidence from our model organism work that this complex is involved in the behavioral response to ethanol, and we had previously observed an association with two members of the SWI/SNF complex and AD in the IASPSAD study (Mathies et al., 2015).

Here, our set-based analyses provide additional evidence for association between allelic variation in subunits of the SWI/SNF chromatin remodeling complex and AD in the COGA adult case-control sample, and with behavior problems in a younger sample of adolescents. We have now observed association between multiple, different, members of the SWI/SNF complex and AD, as well as a genetically related developmental precursor to AD, in three independent human populations. As hypothesized, secondary analyses of the individual genes in the set indicated that it was not always the same genes contributing to the association signal observed with the complex. In the IASPSAD sample, SWI/SNF complex members *SMARCA2* and *BRD7* were associated with AD (Mathies et al., 2015). In COGA, we found that the strongest association signals came from *SS18L1*, *SMARCD1*, *BRD7*, *SMARCB1* and *BCL11A*. When we examined the Spit for Science sample, we found that the strongest signals came from *ACTB*, *ARID2*, *BCL11A*, *BCL11B*, *BCL7B*, *BCL7C*, *DPF2*, and *DPF3*. This combination of data provides growing support for the involvement of SWI/SNF chromatin remodeling in the development of AD. Importantly, our analyses indicate that association should be evaluated at the level of the complex, which is made up of the protein products of multiple genes, and that variation in different genes may be altering SWI/SNF activity across different samples.

How do SWI/SNF complex variants influence both the liability to develop AD in adults and antisocial behavior in adolescents? In current models of AD, a significant component of the genetic liability to develop AD in adults is shared with the genetic components that influence antisocial behavior, impulsivity, and conduct disorders in younger people (Young et al., 2000). We found that the SWI/SNF gene complex impacted AD in an affected adult

sample, and influenced adolescent antisocial behavior in a younger community-based sample. There are two major models to explain how these phenotypes may be related to SWI/SNF: First, variation in the SWI/SNF complex may have effects on nervous system function that are manifested in youth as a predisposition to conduct disorders. Those conduct phenotypes may themselves predispose people to developing AD when they are older and alcohol is readily available. In this case, the effects on AD liability are a consequence of the effects on conduct phenotypes in adolescents, and there are data that support this model (Cho et al., 2014). A second possibility is that there may be shared or distinct effects of SWI/SNF on nervous system function that are manifested in youth as a predisposition to conduct disorders and are independently revealed in adults as an increased liability to develop AD. Importantly, these models are not mutually exclusive, and in the complex landscape of genetic effects on these human behavioral phenotypes, both mechanisms may be working simultaneously.

Our data currently cannot distinguish between these and other possible models. However, the original observations that led to the current studies do suggest that the effects of variation in SWI/SNF complex members on AD may be, at least in part, through the modulation of the physiological response to the drug itself. We previously found that in the model organism *C. elegans*, the acute physiological response to alcohol is altered in animals with altered SWI/SNF function. Animals with loss of function of the BAF complex have decreased initial sensitivity to ethanol, while loss of function of the PBAF complex eliminates the ability of animals to develop AFT to ethanol (Mathies et al., 2015). Although the direct relationship between acute ethanol response phenotypes in *C. elegans* and human AD is not clear, empirically, a finding that a gene has an effect on acute alcohol response phenotypes in invertebrate model organisms very strongly predicts that variation in that gene will be implicated in human AD (Grotewiel and Bettinger, 2015). This empirically observed relationship between genes affecting acute alcohol responses in model organisms and AD in humans strongly suggests that at least some shared molecular mechanisms influence physiological responses to the drug and development of AD. That said, AD is frequently comorbid with antisocial behavior, creating difficulty teasing apart these phenotypes in human genetic analyses. Secondary analyses of log-transformed DSM-IV adult antisocial personality disorder symptom counts in the COGA AD case-control sample yielded a trend toward association with the gene set ($p=0.098$) despite this being a non-ideal test.

SWI/SNF complexes have important and diverse actions during development (Ho and Crabtree, 2010). They are important in the regulation of neuronal development (Son and Crabtree, 2014), where they are required for neural tube closure and the regulation of brain size in mouse (Bultman et al., 2000, Kim et al., 2001). Furthermore, there is strong evidence in humans for functions of SWI/SNF in the nervous system. Recently, several mutations in a member of the SWI/SNF complex, *ARID2*, were identified in individuals with intellectual disability (Shang et al., 2015). Additionally, a transcription factor (ADNP) that directly interacts with the SWI/SNF complex is mutated in syndromic autism (Helsmoortel et al., 2014, Vandeweyer et al., 2014).

It is well established that mutations in different genes encoding proteins that act together can cause the same genetic disorder in humans. In the case of the SWI/SNF complex, variation

in five different BAF genes, *SMARCB1*, *SMARCA4*, *SMARCE1*, *ARID1A*, and *ARID1B*, has been linked to Coffin-Siris Syndrome (CSS), a sporadic intellectual disability syndrome (Santen et al., 2012, Tsurusaki et al., 2012, Tsurusaki et al., 2014). Furthermore, in 87% of CSS patients studied, a mutation in a BAF complex subunit was identified. Together, these data underscore how mutations in different genes encoding members of the same SWI/SNF protein complex can cause similar clinical outcomes.

SWI/SNF complexes have demonstrated functions in differentiated cells. These complexes are required in differentiated neurons for dendritic outgrowth, synaptic plasticity, and memory (Vogel-Ciernia et al., 2013, Olave et al., 2002, Wu et al., 2007, Staahl et al., 2013). Of particular interest in this study was our finding that allelic variation in *SS18L1* is associated with AD. *SS18L1* encodes CREST, which is found specifically in SWI/SNF complexes biochemically purified from differentiated neurons (Fig. 1; Staahl et al., 2013), and is required for dendritic outgrowth (Aizawa et al., 2004). Together, these data suggest that the SWI/SNF complex members identified in our association studies have a clear potential to influence important biological events underlying behavioral problems and the development of AD, because they are functional during both adolescence and adulthood at the place and time during which relevant events would be expected to occur with disease progression.

What molecular mechanisms might underlie how allelic variation in members of the SWI/SNF complex influence antisocial behavior and progression to AD? Because SWI/SNF complexes remodel chromatin structure, they alter gene expression by changing the accessibility of regulatory sequences to the transcriptional machinery. We speculate that allelic variation in these chromatin regulators may result in important changes in their function, either by subtly changing the strength or specificity of protein interactions or enzymatic activity, or by altering the interaction with specific DNA regulatory elements. An alternative mechanism may be that genetic variation may alter the levels of expression of the SWI/SNF component. In any of these cases, such variation could have important effects on the transcriptional regulation of downstream targets of SWI/SNF, either by increasing or decreasing the expression of the target sequences. We anticipate that these targets include the mediators of both of these phenotypes in the brain. Our findings that several SWI/SNF complex members are associated with AD in different human populations and with antisocial behavior in a younger, community sample, that represents a genetically-linked developmental precursor phenotype, argue strongly for efforts to identify the downstream targets of SWI/SNF that are important for mediating these important phenotypes.

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Figure 1. SWI/SNF chromatin remodeling complexes

A. SWI/SNF complexes result from the combination of core (dark grey), common accessory (light grey), and unique accessory (stipple/PBAF or white/BAF) subunits. More than one gene encodes different versions of many of the subunits: the core ATPase subunit is encoded by *SMARCA2* (BRM) or *SMARCA4* (BRG1); BAF250 is encoded by *ARID1A* and *ARID1B*; BAF155 and BAF170 encode interchangeable core subunits; BAF45A is encoded by *PHF10* and BAF45B-D are encoded by *DPF1*, *DPF2* and *DPF3*; BAF53 is encoded by *ACTL6A* and *ACTL6B*; BAF60 is encoded by *SMARCD1*, *SMARCD2*, and *SMARCD3*; BCL7 is encoded by *BCL7A*, *BCL7B*, and *BCL7C*; BCL11 is encoded by *BCL11A* and *BCL11B*; SS18 and CREST are encoded by *SS18* and *SS18L1*, respectively. B. BAF complexes purified from neural progenitors (npBAF) and differentiated neurons (nBAF) contain different SWI/SNF subunits; subunits that differ are highlighted with bold lines. npBAF contains BAF53A, BAF45A or BAF45D, and SS18. nBAF contains BAF53B, BAF45B, and CREST.

Table 1
Gene-based tests of association with alcohol dependence in the COGA case/control sample

Gene	Protein	NSNP	NSIG	ISIG	p-value
<i>ACTB</i>	ACTIN	4	0	0	1.000
<i>ACTL6A</i>	BAF53A	24	3	2	0.163
<i>ACTL6B</i>	BAF53B	16	0	0	1.000
<i>ARID1A</i>	BAF250A	116	4	3	0.342
<i>ARID1B</i>	BAF250B	810	19	9	0.957
<i>ARID2</i>	BAF200	119	2	1	0.712
<i>BCL11A</i>	CTIP1	153	5	3	0.038*
<i>BCL11B</i>	CTIP2	150	2	2	0.739
<i>BCL7A</i>	BCL7A	57	7	3	0.262
<i>BCL7B</i>	BCL7B	59	1	1	0.042*
<i>BCL7C</i>	BCL7C	11	0	0	1.000
<i>BRD7</i>	BRD7	85	3	1	0.021*
<i>BRD9</i>	BRD9	71	2	2	0.315
<i>DPE1</i>	BAF45B	30	0	0	1.000
<i>DPE2</i>	BAF45D	36	11	1	0.066
<i>DPE3</i>	BAF45C	523	28	10	0.303
<i>PBRM1</i>	PBRM1	262	36	2	0.300
<i>PHF10</i>	BAF45A	37	0	0	1.000
<i>SMARCA2</i>	hBRM	289	22	11	0.233
<i>SMARCA4</i>	BRG1	280	11	1	0.928
<i>SMARCB1</i>	BAF47/INI1	202	136	5	0.042*
<i>SMARCC1</i>	BAF155	207	14	6	0.184
<i>SMARCC2</i>	BAF170	10	0	0	1.000
<i>SMARCD1</i>	BAF60A	19	3	1	0.016*
<i>SMARCD2</i>	BAF60B	20	0	0	1.000
<i>SMARCD3</i>	BAF60C	77	0	0	1.000
<i>SMARCE1</i>	BAF57	33	2	2	0.405
<i>SS18</i>	SS18	119	3	3	0.294

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Gene	Protein	NSNP	NSIG	ISIG	p-value
<i>SS18L1</i>	CREST	123	52	2	0.008**

Note: For each gene, NSNP= number of SNPs; NSIG= number of significant SNPs; ISIG= number of independent significant SNPs.

* p-value <0.05;
** p-value 0.01.

Accordingly, test statistics are corrected for multiple testing with each gene, but not across all genes. We note that these analyses are presented as secondary analyses to supplement the primary test of the overall gene set and provide insight into the genes in the set most strongly driving the overall association signal for the SWI/SNF complex.

Table 2
Gene-based tests of association between SWI/SNF genes and externalizing behavior in the S4S sample

Gene	Protein	NSNP	NSIG	ISIG	p-value
<i>ACTB</i>	ACTIN	4	3	1	0.007**
<i>ACTL6A</i>	BAF53A	22	0	0	1.000
<i>ACTL6B</i>	BAF53B	6	0	0	1.000
<i>ARID1A</i>	BAF250A	53	0	0	1.000
<i>ARID1B</i>	BAF250B	270	30	4	0.272
<i>ARID2</i>	BAF200	71	20	2	0.042*
<i>BCL11A</i>	CTIP1	53	2	1	0.003**
<i>BCL11B</i>	CTIP2	98	42	10	0.002**
<i>BCL7A</i>	BCL7A	29	0	0	1.000
<i>BCL7B</i>	BCL7B	4	2	1	0.039*
<i>BCL7C</i>	BCL7C	1	1	1	0.008**
<i>BRD7</i>	BRD7	46	0	0	1.000
<i>BRD9</i>	BRD9	3	0	0	1.000
<i>DPF1</i>	BAF45B	0	0	0	NA
<i>DPF2</i>	BAF45D	1	1	1	0.015*
<i>DPF3</i>	BAF45C	231	118	10	0.001***
<i>PBRM1</i>	PBRM1	169	0	0	1.000
<i>PHF10</i>	BAF45A	23	0	0	1.000
<i>SMARCA2</i>	hBRM	140	12	5	0.059
<i>SMARCA4</i>	BRG1	39	2	1	0.250
<i>SMARCB1</i>	BAF47/INI1	185	0	0	1.000
<i>SMARCC1</i>	BAF155	116	0	0	1.000
<i>SMARCC2</i>	BAF170	0	0	0	NA
<i>SMARCD1</i>	BAF60A	2	1	1	0.071
<i>SMARCD2</i>	BAF60B	15	0	0	1.000
<i>SMARCD3</i>	BAF60C	17	0	0	1.000
<i>SMARCE1</i>	BAF57	15	0	0	1.000

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Gene	Protein	NSNP	NSIG	ISIG	p-value
SS18	SS18	76	3	2	0.089
SS18L1	CREST	63	0	0	1.000

Note: For each gene, NSNP= number of SNPs; NSIG= number of significant SNPs; ISIG= number of independent significant SNPs.

* *p*-value 0.05;
** *p*-value 0.01;
*** *p*-value 0.001.

Accordingly, test statistics are corrected for multiple testing with each gene, but not across all genes. We note that these analyses are presented as secondary analyses to supplement the primary test of the overall gene set and provide insight into the genes in the set most strongly driving the overall association signal for the SWI/SNF complex.