EMPIRICAL ARTICLE

Genetic Variants Associated with Disordered Eating

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ABSTRACT

Objective: Although the genetic contribution to the development of anorexia nervosa (AN) has long been recognized, there has been little progress relative to other psychiatric disorders in identifying specific susceptibility genes. Here, we have carried out a genome-wide association study on an unselected community sample of female twins surveyed for eating disorders.

Method: We conducted genome-wide association analyses in 2,564 female twins for four different phenotypes derived from self-report data relating to lifetime presence of 15 types of disordered eating: AN spectrum, bulimia nervosa (BN) spectrum, purging via substances, and a binary measure of no disordered eating behaviors versus three or more. To complement the variant level results, we also conducted gene-based association tests using VEGAS software.

Results: Although no variants reached genome-wide significance at the level of $p < 10^{-8}$, six regions were suggestive ($p < 5 \times 10^{-7}$). The current results implicate the following genes: CLEC5A, LOC136242, TSHZ1, and SYTL5 for the AN spectrum phenotype; NT5C1B for the BN spectrum phenotype; and ATP8A2 for the disordered eating behaviors phenotype.

Discussion: As with other medical and psychiatric phenotypes, much larger samples and meta-analyses will ultimately be needed to identify genes and pathways contributing to predisposition to eating disorders. © 2013 by Wiley Periodicals, Inc.

Keywords: genes; anorexia nervosa; genome-wide association study

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Introduction

Twin studies suggest that around 60% of the variance in risk for developing anorexia nervosa (AN) and disordered eating is due to genetic factors,[1–3] with more variable estimates attributed to bulimia nervosa (BN, ranging from 28[4] to 83%[5]). Linkage studies identified regions on chromosomes 1, 2, 4, and 13 as suggestive of linkage for AN[6,7] with follow-up significant association of the delta opioid receptor (OPRD1) and serotonin (5-HT) receptor 1D (HTR1D) genes, both on chromosome 1.[8] For BN, significant linkage was observed on chromosome 10 and another region on chromosome 14 was suggestive for genome-wide linkage.[9] Well over 200 candidate gene association studies of eating disorders have been conducted, focusing primarily, but not exclusively, on serotonergic, dopaminergic, and appetite regulatory genes; however, largely because of an overreliance on small samples, replication has not been universal and clear conclusions remain elusive (Trace et al., submitted).

The current preferred approach to rectifying the nebulous results emerging from a litany of underpowered studies is to boost power through meta-analyses of multiple genome-wide association studies (GWAS). In contrast to candidate gene association studies that focus on prespecified genes of interest, GWAS represent an unbiased scan of the entire genome for common genetic variation in cases versus healthy controls. To date, three GWAS investigations[10–12] have been published for eating disorders; none of which has yielded genome-wide significant single-nucleotide

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FIGURE 1. Flow diagram depicting sample and data used in the GWAS.

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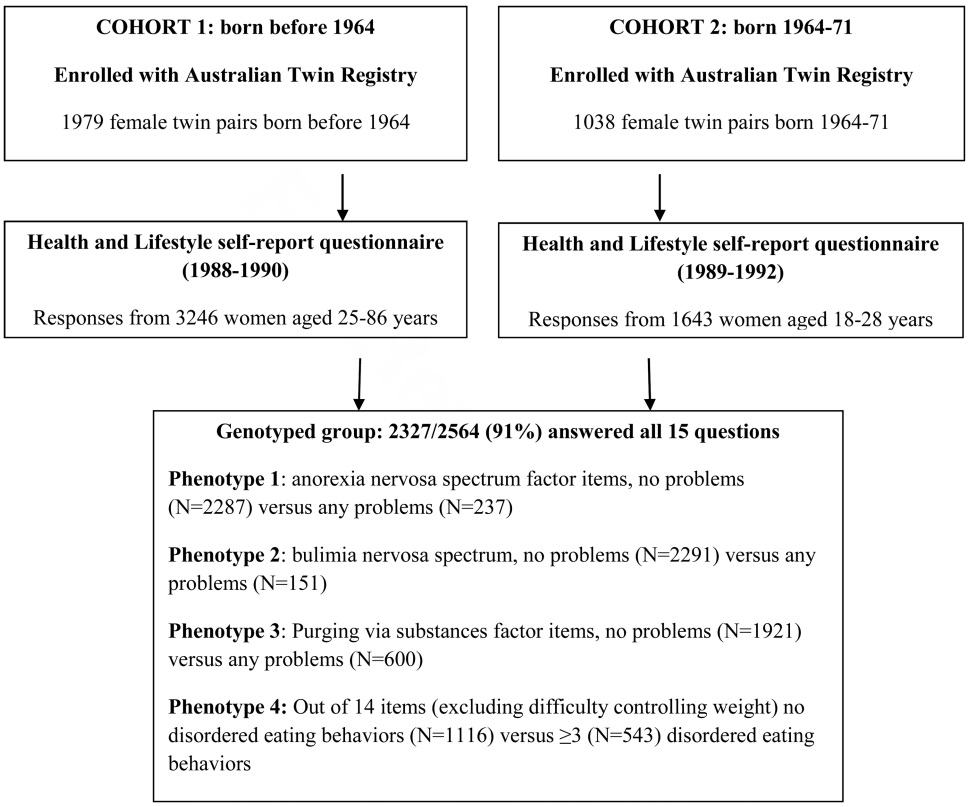


polymorphisms (SNPs), where adequate significance is set at $p < 10^{-8}$, as suggested by Li et al.[13] The first, from the Japanese Genetic Research Group for Eating Disorders,[10] showed the strongest associations for AN in 320 cases and 341 controls at 1q41 (with the most significant association observed at SNP rs2048332) and 11q22 (associated with four SNP markers, rs6590474, D11S0268i, rs737582, and rs7947224). The second study of 1,033 AN cases and 3,733 pediatric controls[11] had top association signals detected near *ZNF804B*, *CSRP2BP*, *NTNG1*, *AKAP6*, and *CDH9*. This latter gene codes for a neuronal cell-adhesion proteins that influences how neurons communicate with each other in the brain and has been associated with autism spectrum disorders. The third study,[12] which examined six eating disorder-related symptoms, behaviors, and personality traits in 2,698 individuals, detected association of eight genetic variants with $p < 10^{-5}$, and an associated meta-analysis showing five SNP markers (and associated genes) met genome-wide significance level: rs6894268 (*RUFY1*), rs7624327 (*CCNL1*), rs10519201 (*SHC4*), rs4853643 (*SDPR*), and rs218361 (*TRPS1*). A further GWAS of AN, conducted by the International Wellcome Trust Case Control Consortium (WTCCC3) on 2,907 patients with AN and 14,860 geographically matched controls, is in progress.[14]

Eating disorders are associated with the highest mortality of any psychiatric disorder.[15–18] Best evidence treatment approaches have been identified for bulimic disorders,[19] but the evidence base for how best to treat AN is weak.[20] There are no medications that are currently considered to be effective in the treatment of AN, and progress in this area has been hampered by a lack of knowledge about the underlying neurobiology of the condition. The clear-cut identification of genomic variation that predisposes to eating disorders can provide the basis for the next generation of research into etiology, treatment, and prevention.

In line with evidence that shows that large-scale collaborative GWAS studies and larger sample sizes can achieve the necessary power to identify specific loci in psychiatric disorders,[21,22] the aim of this study is to contribute to the accumulation of a larger sample size related to disordered eating. This

TABLE 1. Endorsement of 15 self-report questionnaire items relating to eating and exploratory factor analysis in the total sample ($N = 6,002$) using varimax rotation of the 15 eating items

Item	>1 Item Answered (%, $N = 6,104$)	Genotyped Females (%, $N = 2,564$)	Factor 1, Anorexia Nervosa Spectrum	Factor 2, Bulimia Nervosa Spectrum	Factor 3, Purging via Substances	Factor 4, Disordered Eating Behaviors
Do you feel that you have difficulty controlling weight?	46.0	47.5	−0.084	−0.08	−0.132	**0.438**
Do you feel you have had problems with disordered eating?	23.9	23.8	0.003	−0.015	−0.138	**0.375**
Do you feel you have been preoccupied with thoughts of food or body weight?	36.9	37.1	−0.04	−0.051	−0.111	**0.402**
Have you ever used any of the following methods to control your body weight?						
Starvation	12.4	11.9	0.055	0.027	0.172	0.076
Excessive exercise	13.6	12.6	0.015	0	0.068	0.164
Laxatives	7.7	7.8	0.013	−0.022	**0.461**	−0.125
Fluid tablets	7.4	7.6	−0.016	−0.08	**0.506**	−0.163
Slimming tablets	16.3	17.4	−0.067	−0.064	**0.324**	0.059
Self-induced vomiting	4.5	3.8	−0.041	**0.28**	0.207	−0.087
Have you ever suffered from or been treated for:						
Binge eating	2.6	2.9	−0.084	**0.455**	−0.139	0.027
Bulimia	1.0	0.9	−0.105	**0.525**	−0.032	−0.102
Eating disorder	3.5	3.3	**0.208**	0.156	−0.09	0.014
Anorexia nervosa	1.8	1.7	**0.301**	0.023	0.014	−0.067
Low body weight	5.0	5.1	**0.426**	−0.148	−0.017	−0.052
Weight loss	5.9	5.8	**0.394**	−0.158	0.003	−0.011

Items loading ≥0.2 are in bold.

study conducted a GWAS of four different phenotypes of disordered eating in an unselected sample of 2,564 female twins in order to further our knowledge of the genomic variation that predisposes to core features of eating disorders. This represents only the fourth published GWAS in eating disorders, and so a secondary aim was to see whether we could achieve any replication with the previously published studies.[10–12]

Method

Participants

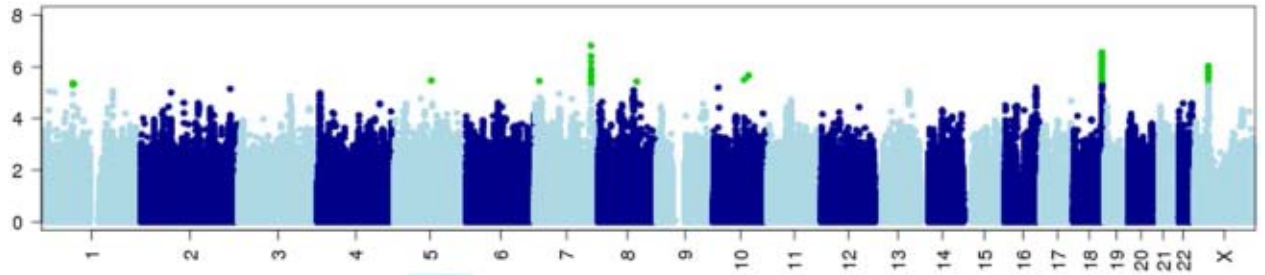
Participants were from the volunteer adult Australian Twin Registry maintained by the National Health and Medical Research Council. These data are from two cohorts of women who completed a mailed questionnaire survey 1988–1992, as shown in Figure 1. The first cohort, born before 1964, has been previously described,[3,23,24] and an examination of their sociodemographic features, including age, marital status, educational background, workforce participation, major lifetime occupation, and religious denomination, suggests that the sample is not notably different from the Australian female population (using data obtained from the Australian Bureau of Statistics between 1986 and 1992). The second cohort included women born between 1964 and 1971 and has also been previously described.[25,26] Most of these twins had been recruited when at school some 10 years earlier. All applicable institutional regulations concerning the ethical use of human volunteers were followed during this research. The final combined sample where there were both phenotypic data for disordered eating and genotypes comprised 2,564 women.

Phenotypes

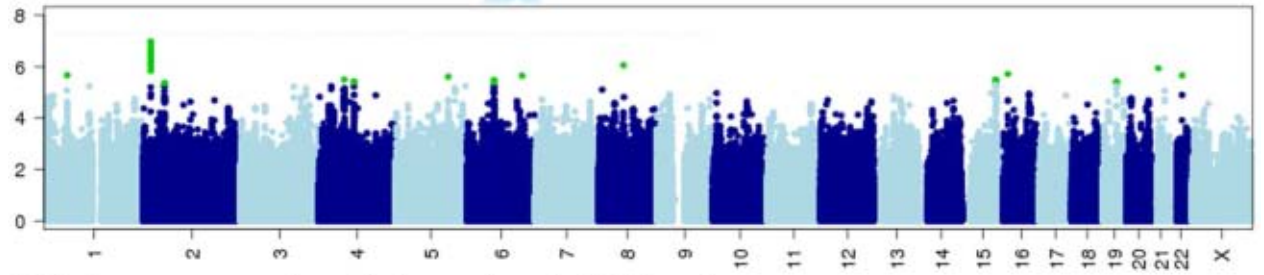
The 1988–1992 surveys mailed to female twins contained five questions assessing disordered eating and these are shown in Table 1. These questions produced a total of 15 variables relating to disordered eating. A previous examination of these items along with two subsequent measures of eating disordered behavior indicated that 60% (95% CI: 50–68) of the variance could be attributed to additive genetic influences.[3] In the younger cohort, a follow-up telephone interview was conducted in 2001–2003 when they were aged 28–40 years (about 10 years after the self-report questionnaire) using the Eating Disorder Examination (EDE[27]) with 1,083 women, indicating a moderate association ($r = .31$ and .38 for Twins 1 and 2, respectively) between the mean number of 16 possible problems endorsed in the self-report questionnaire and total number of six possible eating disorder behaviors endorsed at interview.[26] Moderate agreement is also obtained between two different interview schedules (including the EDE) assessing eating disorders 18–24 months apart, achieving a kappa value of <0.60.[28]

As shown in Figure 1, four different phenotypes relating to disordered eating were examined. The first three

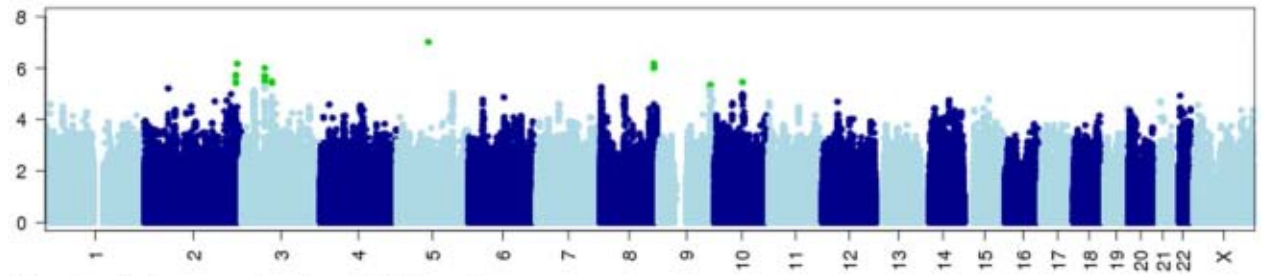
FIGURE 2. Manhattan plots: 1000 Genomes-based dosage scores (SNPs with $R^2 > 0.3$ and MAF > 0.02) for the four disordered eating phenotypes analyzed. Vertical scale is $-\log_{10}(p)$; $p < 10^{-8}$ is considered significant. Horizontal scale is hg19/Build 37 position. Green for SNPs with $p < 10^{-5}$, otherwise alternate colors for alternate chromosomes. Anorexia nervosa spectrum factor case/control (four items). Bulimia nervosa spectrum factor case/control (three items). Purging factor case/control (three items). Disordered eating 14 item case/control. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



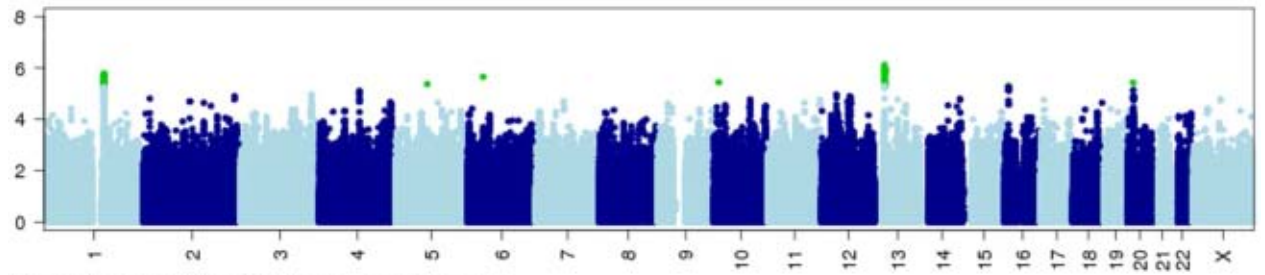
Anorexia nervosa spectrum factor case/control (4 items)



Bulimia nervosa spectrum factor case/control (3 items)



Purging factor case/control (3 items)



Disordered eating 14 item case/control

phenotypes were derived from an exploratory factor analysis of the 15 variables for all available data, whether women had been genotyped or not. The resultant factors are shown in Table 1, where items with factor loadings $\geq$0.2 are highlighted. Of interest to the current investigation were those factors that related to disordered eating, namely Factor 1 (AN spectrum), Factor 2 (BN spectrum), and Factor 3 (purging via substances).

For the fourth phenotype (disordered eating behaviors), the item relating to "difficulty controlling weight" was excluded as it was endorsed so widely that it was considered not to be indicative of disordered eating but

rather of the normative struggle many women feel that they have with their weight. The remaining 14 items were reduced to a binary variable, where women who endorsed "no" for all items were grouped as "controls," and women who endorsed three or more problems were grouped as "cases."

Genotyping

Genotypes were drawn from an existing QIMR Genetic Epidemiology Laboratory GWAS data for >19,000 individuals (comprised of twin pairs, nuclear families, or singletons), which integrates data from eight batches of genotyping obtained using standard Illumina chips. The subset used here includes individuals typed with the 610K-quad chip (1,138 individuals), 370K or 370K-duo chips (738 individuals), or the Illumina 317K chip (644 individuals); 316 individuals were genotyped on more than one chip either for deliberate QC reasons or to obtain higher coverage than an early-generation chip used previously. Individual genotypes were eliminated where they conflict between monozygotic twins or repeat genotypings, as well as (within each family) all genotypes for markers with Mendelian errors. All twin-family members were used in the genetic analysis, taking account of their relatedness (see below).

Within each batch, genotypes were called using the Genotyping Module in Beadstudio and then exported. Cleaning was later performed (a) per-SNP to remove SNPs with (1) minor allele frequency (MAF) < 1%; (2) call rate < 95%; (3) mean GenCall score < 0.7; or (4) Hardy-Weinberg p-value < 10^{-6} and (b) per-individual to remove individuals with (in their batch) a call rate <95% or other obvious quality issues; or (c) in the integrated dataset, having (1) an unresolvable sample mix-up, zygosity, or pedigree issue after archival investigation of outlier families from IBS and IBD-based relatedness checks or (2) being an ancestry outlier based on lying >6sd from the PC1 or PC2 mean for Europeans in a Principal Components Analysis run in SMARTPCA v3, with all HapMap Phase II/III and non-QIMR EUTWIN populations used as a training set. The dataset contains verified pedigree data for all individuals barring a small number of distant relationships (typical π-hat < 0.1).

Measured genotypes for the ~281,000 SNPs passing QC in all genotyping batches were used to impute to 1000 Genomes SNPs (Release 20100804) via the recommended prephasing method in MACH and Minimac,[29] using the publicly available EUR-phased haplotypes as reference panel (from the formatted 1000 Genomes haplotype files supplied by the software authors' web site, for this purpose). In all, 7,262,007 SNPs were initially analyzed (this is after the R^2 quality control test but not the MAF test), and 6,150,213 SNPs remained after filtering out those with MAF < 2%. As people genotyped already had their zygosity assessed previously in various ways, no twin pairs needed to be discarded due to discordance revealed by genotyping. The number of twins passing quality control varied by phenotype: 2,524 for the AN spectrum, 2,442 for the BN spectrum, 2,521 for purging via substances, 1,659 for the 14-item disordered eating score.

Statistical Analysis

Four case/control phenotypes were analyzed. To allow for both developmental and secular cohort effects on these phenotypes, we included age, age^2, cohort, age × cohort, and age^2 × cohort as covariates. Analyses were conducted using MERLIN-OFFLINE, which implements a total test of association using allele dosage scores while explicitly modeling the relationship structure within our MZ and DZ twin families.[30] Variants with poor imputation accuracy (R^2 < 0.3) and rare variants (MAF < 0.02) were excluded from analyses.

Gene-based association tests were run on the association results for common variants using VEGAS[31] (v0.8.27). Note that VEGAS as currently configured identifies SNPs within genes based on the gene boundaries as defined by Build 36 (hg18) coordinates, and returns results in these coordinates. VEGAS results reported here have been converted to Build 37 (hg19) for consistency with other quoted positions. Because of software limitations, only SNPs found in HapMap II genotypes were analyzed, and results for the X chromosome are not available from VEGAS.

Results

Genome-Wide Association of SNP Data

The results of the GWAS analyses for each of our four binary eating disorder variables are summarized in the Manhattan plots presented in **Figure 2**. LD pruned results for variants $p < 10^{-5}$ are provided in **Table 2**. The top 100 gene-based results from VEGAS are listed in **Table 3**.

Many of those with one (or few) associated SNPs per peak appear to represent false-positive signals, as either they are not in LD with adjoining SNPs or are in LD but adjoining SNPs are also not associated. Peaks shown with ≤2 SNPs in **Table 2** were all manually inspected to ascertain if they contained a signal off the listed SNP(s). In the majority of instances, there is no association signal off the listed SNP(s) even without applying the "MAF ≥ 2%" filter to association results. In others there are other mildly associated SNPs with no signal in between. The most notable such exceptions have been footnoted in **Table 2**.

The initial GWAS analyses yielded a number of suggestive association signals, although none

TABLE 2. Single-SNP association peaks for individual 1000 Genomes SNPs

Chr	Start (bp, Build 37)	End (bp, Build 37)	# SNPs ($p < 10^{-5}$)	SNP with Lowest p	Lowest p-Value	Effect Allele	Other Allele	Effect = Beta	SE	Imputation R^2	Imputed Allele Freq (%)	Genes at These SNPs	Genes Within (approx) ± 50 kbp
Anorexia nervosa syndrome factor case/control													
7	141450588	1416658110	65	rs145241704	1.51*E*−07	T	G	−0.143	0.027	0.542	95.2	CLEC5A; LOC136242	KIAA1147; MGAM; OR9A4; SSBP1; TAS2R3; TAS2R4; TAS2R5; TAS2R38; WEE2
18	72986495	73072779	26	rs62090893	2.84*E*−07	G	A	−0.085	0.017	0.876	92.1	TSHZ1	C18orf62
X	37905642	38009352	55	rs56156506	9.51*E*−07	A	T	−0.053	0.011	0.994	81.3	SYTL5	
10	87692965	87694292	2	rs76765968	2.21*E*−06	T	C	−0.064	0.014	0.716	85.6	GRID1	
10	77298609		1	rs2043090	3.26*E*−06	A	G	−0.119	0.026	0.727	95.9		
5	94148538		1	rs469339	3.45*E*−06	A	G	−0.144	0.031	0.875	97.7	MCTP1	
7	12193432		1	rs114945094	3.60*E*−06	G	A	−0.135	0.029	0.464	95.9		
8	87874292	96504472	3	rs77742018	3.83*E*−06	A	G	−0.117	0.025	0.609	94.6		CNBD1
1	79218940	79227956	7	rs1937020	4.45*E*−06	T	C	−0.041	0.009	1.000	68.1		
10	12702569		1	rs75263140	6.44*E*−06	A	G	−0.172	0.038	0.435	97.4	CAMK1D	
16	79184753	79186886	2	rs8050187	6.57*E*−06	T	C	−0.044	0.010	0.939	73.6	WWOX	
2	223353446		1	rs17496827	7.29*E*−06	C	A	−0.042	0.009	0.767	55.0	SGPP2	
1	180128044	180130723	2	rs55946907	8.54*E*−06	C	T	−0.066	0.015	0.888	90.1	QSOX1	CEP350
13	85548207	85549736	2	rs9531686	8.90*E*−06	T	G	−0.038	0.008	0.995	57.1		
1	19206334		1	rs28441017	8.93*E*−06	G	A	−0.086	0.019	0.335	82.7	ALDH4A1	TAS1R2
1	32668428		1	rs6425793	9.63*E*−06	A	G	−0.066	0.015	0.357	69.7	CCDC28B	C1orf91; DCDC2B; EIF3I; FAM167B; IQCC; KPNA6; LCK; TXLNA
Bulimia nervosa syndrome factor case/control													
2	18794610	18867580	43	rs1445130	1.08*E*−07	A	G	−0.056	0.01	0.974	86.4		NT5C1B
8	63258917		1	rs142014203	8.83*E*−07	T	G	−0.126	0.026	0.765	97.4	NKAIN3	
21	19531442		1	rs77600076	1.17*E*−06	A	C	−0.124	0.025	0.588	97.1		CHODL; TMPRSS15
16	11386960		1	rs117096873	1.95*E*−06	C	T	−0.129	0.027	0.654	97.4		PRM1; PRM2; PRM3; SOCS1; TNP2
1	58288972	58319828	2	rs985795	2.22*E*−06	T	G	−0.094	0.020	0.652	94.6	DAB1	
22	31438361		1	rs111383589	2.25*E*−06	C	T	−0.087	0.018	0.383	89.2		SMTN
6	138426032		1	rs1556640	2.33*E*−06	T	C	−0.075	0.016	0.437	88.0	PERP	
5	134321546		1	rs299362	2.52*E*−06	A	G	−0.062	0.013	0.766	88.6	CATSPER3	PITX1; PCBD2
4	63845629	63893278	27	rs145379083	3.26*E*−06	G	A	−0.037	0.008	0.813	51.0		
15	85699207	85719207	9	rs8040855	3.32*E*−06	C	G	0.035	0.007	0.972	63.4		PDE8A
6	67645244	67653279	6	rs28631020	3.45*E*−06	G	A	−0.080	0.017	0.718	92.5		
19	29897537	29918577	4	rs12986207	3.90*E*−06	G	A	−0.044	0.01	0.963	81.7		VSTM2B
4	88053335	88126797	4	rs115694618	3.91*E*−06	A	G	−0.123	0.027	0.760	97.9	AFF1; KLHL8	C4orf36; HSD17B13; HSD17B11
2	53727034	53756542	4	rs56148675	4.50*E*−06	T	C	−0.076	0.017	0.905	94.2		
5	177808675		1	rs2910124	5.80*E*−06	C	T	−0.059	0.013	0.610	85.8	COL23A1	
1	114226143		1	rs61742849	5.82*E*−06	G	A	−0.179	0.039	0.326	97.5	MAGI3	PHTF1
4	31152756	31156178	3	rs74879986	5.86*E*−06	G	A	−0.140	0.031	0.619	97.5		
3	133260874		1	rs11708304	6.09*E*−06	C	T	−0.059	0.013	0.598	85.3		CDV3
15	87710066	87710066	10	rs8024343	6.14*E*−06	A	T	−0.045	0.010	0.901	83.1		
5	150585867	150596254	12	rs7724774	6.93*E*−06	G	A	−0.054	0.012	0.899	88.4	CCDC69	GM2A
3	163855069		1	rs78661745	7.15*E*−06	C	T	−0.068	0.015	0.645	90.8		
8	10086411		1	rs6999631[a]	8.01*E*−06	C	G	−0.090	0.020	0.854	96.5	MSRA	

TABLE 2. Continued.

Chr	Start (bp, Build 37)	End (bp, Build 37)	# SNPs ($p < 10^{-5}$)	SNP with Lowest p	Lowest p-Value	Effect Allele	Other Allele	Effect = Beta	SE	Imputation R^2	Imputed Allele Freq (%)	Genes at These SNPs	Genes Within (approx) ± 50 kbp
21	34369761		1	rs117124364	8.93*E*−06	C	T	−0.160	0.036	0.374	97.7		OLIG2
Purging via substances factor case/control													
5	80406566		1	rs138206701	9.65*E*−08	A	G	−0.327	0.061	0.535	98.0		RASGRF2
8	134771894	134781276	3	rs74566133	6.65*E*−07	C	T	−0.249	0.050	0.465	96.9		
2	232298076		1	rs12475512	6.82*E*−07	G	A	0.108	0.022	0.349	54.3		NCL; PTMA; PDE6D
3	58101471	58138528	10	rs13077017	1.00*E*−06	C	T	−0.073	0.015	0.933	71.0	FLNB	DNASE1L3
2	228667258	228672579	6	rs10175070	1.94*E*−06	A	G	0.124	0.026	0.341	75.0	SPHKAP; CCL20	
3	76261724	76261820	2	rs1516459	3.37*E*−06	C	T	−0.270	0.058	0.383	96.8		
10	70014230		1	rs10998035	3.61*E*−06	C	T	−0.151	0.033	0.775	94.5	ATOH7	
9	130503612	130517973	5	rs514024	4.51*E*−06	A	G	0.061	0.013	0.999	57.2	PKN3	SET; WDR34; ZDHHC12; ZER1
8	3156220	3156271	3	rs142816172	5.60*E*−06	C	T	−0.273	0.060	0.524	97.6	CSMD1	
2	60126311		1	rs145433814	6.25*E*−06	G	A	−0.239	0.053	0.559	97.6		
3	31036738	31042738	8	rs1506203	7.71*E*−06	G	T	−0.083	0.018	0.952	84.9	GADL1	
5	140668925		1	rs113951537	9.77*E*−06	G	T	−0.163	0.037	0.875	96.2		PCDHGA[b]; PCDHGB[b]; SCL25A2; TAF7
14-Item case/control disordered eating behaviors													
13	25994044	26022597	43	rs7322916	7.68*E*−07	G	A	0.089	0.018	0.899	50.1	ATP8A2	
1	152295942	152407207	82	rs3120667	1.66*E*−06	A	G	−0.118	0.025	0.956	84.5	FLG; FLG2; CRNN	
6	39117698		1	rs2115200	2.25*E*−06	T	G	0.098	0.021	0.980	76.8		C6orf64; KCNK5
10	12875208		1	rs10906233	3.65*E*−06	C	T	−0.288	0.062	0.953	97.9		CAMK1D
20	15120744	15121081	2	rs11087123[c]	3.83*E*−06	A	G	−0.12	0.026	0.536	73.8	MACROD2	
5	80406566		1	rs138206701	4.25*E*−06	A	G	−0.425	0.092	0.535	98.0	RASGRF2	
16	10663627	10673844	7	rs2221433	4.99*E*−06	G	T	−0.087	0.019	0.926	68.2	EMP2	TEKT5
4	100395414	100418353	10	rs148915469	7.90*E*−06	C	T	−0.279	0.062	0.953	97.9		ADH7; C4orf17

Peaks highlighted in bold are plotted in Figure 3.

[a] rs6999631 (Bulimia case/control) is 1235 bp from SNP rs141680122 ($p \sim 8.0 \times 10^{-10}$, MAF ∼ 1.1%) which fails our 2% MAF filter. However, there is no apparent association signal apart from these two SNPs even without that filter.

[b] Many genes/isoforms in that family.

[c] rs11087123 (14-item case/control) is in a wide block of associated SNPs down to $p \sim 1.3 \times 10^{-5}$ (40 with $p \leq 10^{-4}$) which fail the p-value filter used here.

TABLE 3. Gene-based associations at $p < 10^{-3}$ [plus other top 100 genes in same block] for each phenotype

			Most Associated Gene in Block			Most Associated HapMap (II) SNP within Most Associated Gene							Other Gene(s) Associated, Top 100 for Phenotype
Chr	Start (bp; hg19/ Build 37)	End (bp)	Gene Name	Gene *p*-Value	# SNPs	SNP Name	*p*-Value	Effect Allele	Other Allele	Effect = Beta	SE	Imputation R^2	Effect Allele Freq (%)	
Anorexia spectrum factor case/control														
7	141536085	141646783	OR9A4	4.30*E*−05	72	rs1285957	1.00*E*−06	C	T	−0.056	0.012	0.968	82.6	LOC136242; CLEC5A
3	130613433	131069303	ASTE1	8.50*E*−05	84	rs13076493	3.34*E*−05	C	T	−0.043	0.010	0.982	78.8	ATP2C1; NEK11
16	29674299	29709314	SPN	1.28*E*−04	28	rs9933310	3.30*E*−05	A	G	0.043	0.010	0.638	58.9	QPRT
10	124320180	124459338	C10orf120	1.89*E*−04	54	rs2421031	4.62*E*−04	T	C	0.048	0.014	0.478	74.0	DMBT1
10	87359311	88495824	LDB3	2.78*E*−04	154	rs2803546	2.79*E*−04	G	A	0.034	0.009	0.843	54.6	OPN4; GRID1
2	74682198	74875164	LOXL3	2.87*E*−04	36	rs17010021	1.00*E*−05	T	A	−0.105	0.024	0.696	95.8	ZNHIT4; WBP1; GCS1; MRPL53; CCDC142; TTC31; LBX2; PCGF1; TLX2; DQX1; AUP1; HTRA2; DOK1; C2orf65
15	80137317	80263643	MTHFS	3.48*E*−04	164	rs1113983	1.30*E*−04	C	A	−0.033	0.009	0.988	63.1	ST20; C15orf37; BL2A1
1	68511644	68516460	DIRAS3	3.88*E*−04	64	rs12069862	5.42*E*−04	G	A	−0.110	0.032	0.406	95.9	
10	102672325	102747272	FAM178A	4.49*E*−04	118	rs11190790	2.02*E*−04	C	A	0.032	0.009	0.999	64.1	SEMA4G; MRPL43
5	118407083	118584822	DMXL1	6.14*E*−04	129	rs4895185	1.69*E*−04	A	G	−0.033	0.009	0.999	66.8	
7	138818523	138874546	TTC26	7.70*E*−04	82	rs7798474	6.90*E*−05	T	G	−0.039	0.010	0.992	75.4	
8	86019376	86132643	LRRCC1	9.53*E*−04	34	rs4150880	1.70*E*−05	A	T	−0.045	0.010	0.912	76.2	LRRCC1; E2F5; C8orf59
4	5822490	5894785	CRMP1	9.67*E*−04	205	rs3774895	2.00*E*−05	T	A	−0.036	0.008	0.981	50.4	
Bulimia nervosa spectrum factor case/control														
5	140682195	140892546	SLC25A2	1.18*E*−04	82	rs10491309	1.67*E*−04	A	G	−0.095	0.025	0.547	96.1	TAF7; PCDHGA1; PCDHGA3
2	42396515	42721237	KCNG3	1.58*E*−04	133	rs1874449	6.30*E*−05	T	G	0.030	0.007	0.926	57.0	EML4; COX7A2L
16	69796273	69997889	LOC348174−1	2.10*E*−04	30	rs904809	4.30*E*−05	G	A	−0.033	0.008	0.878	67.6	WWP2
3	38035077	38071133	PCLD1	2.48*E*−04	85	rs6809649	2.44*E*−04	T	C	0.036	0.010	0.957	82.2	VILL
1	10093015	10480201	KIF1B	2.54*E*−04	173	rs12131785	1.50*E*−05	C	T	−0.042	0.010	0.752	75.4	PGD; UBE4B
7	100218038	100395419	POP7	3.02*E*−04	42	rs221795	5.50*E*−05	T	C	−0.029	0.007	1.000	65.0	GNB2; GIGYF1; EPO; TFR2; ACTL6B; ZAN
14	69517641	69709072	EXDL2	3.56*E*−04	87	rs4902704	1.63*E*−04	C	G	−0.028	0.007	0.969	61.1	WDR22
5	169064292	169510381	LOC100131897	4.71*E*−04	300	rs30080	4.70*E*−05	C	G	−0.030	0.007	0.997	60.7	DOCK2
5	175511908	175543457	FAM153B	5.58*E*−04	30	rs7443800	3.22*E*−04	G	A	−0.027	0.007	0.943	57.5	
22	40742503	40806293	ADSL	5.66*E*−04	52	rs2235318	2.68*E*−04	C	T	−0.037	0.010	0.866	81.4	SGSM3
21	27096790	27144771	GABPA	5.66*E*−04	81	rs10482968	2.41*E*−04	C	A	−0.043	0.012	0.959	89.3	ATP5J
14	99947738	99977852	CCNK	7.06*E*−04	87	rs4905848	9.78*E*−04	G	A	−0.026	0.008	0.796	48.4	CCNK
1	225965530	225978164	SRP9	7.29*E*−04	101	rs12118223	6.34*E*−04	A	T	−0.061	0.018	0.412	90.4	SRP9
7	138728265	138874546	ZC3HAV1	7.56*E*−04	123	rs1814170	3.40*E*−05	A	T	−0.056	0.014	0.797	90.2	TTC26
1	23755055	23886322	E2F2	8.03*E*−04	64	rs3218148	1.97*E*−04	A	G	−0.028	0.008	0.905	54.7	DDEFL1; ID3
2	228474805	228497888	DKFZp547H025	8.18*E*−04	158	rs2396468	1.47*E*−04	A	C	−0.046	0.012	0.786	87.1	C2orf83
19	49588464	49715093	LIN7B	8.35*E*−04	71	rs8044	1.02*E*−03	G	T	−0.024	0.007	0.979	60.6	SNRP70; FLJ10490; PPFIA3; HRC; TRPM4
16	31470316	31540124	TGFB1I1	8.98*E*−04	44	rs7187900	7.53*E*−04	A	G	−0.025	0.007	0.956	48.5	ARMC5; SLC5A2; C16orf58; ERAF
15	74528666	74660081	CCDC33	9.55*E*−04	184	rs2930313	1.23*E*−04	A	G	−0.059	0.015	0.690	91.1	CYP11A1
15	43568478	43941039	LCMT2	9.58*E*−04	62	rs2412779	3.33*E*−04	A	G	−0.043	0.012	0.917	89.8	ADAL; ZSCAN29; TUBGCP4; TP53BP1; HISPPD2A; CKMT1B; STRC; CATSPER2; MAP1A; TGM7
Purging via substances factor case/control														
9	130374567	130617047	SH2D3C	3.00*E*−06	78	rs514024	5.00*E*−06	A	G	0.061	0.013	0.999	57.2	STXBP1; C9orf117; PTRH1; TTC16; TOR2A; CDK9; FPGS; ENG

TABLE 3. Continued.

Chr	Start (bp; hg19/ Build 37)	End (bp)	Most Associated Gene in Block: Gene Name	Gene *p*-Value	# SNPs	Most Associated HapMap (II) SNP within Most Associated Gene: SNP Name	*p*-Value	Effect Allele	Other Allele	Effect = Beta	SE	Imputation R^2	Effect Allele Freq (%)	Other Gene(s) Associated, Top 100 for Phenotype
1	229406878	229478688	C1orf96	9.90*E*−05	84	rs163771	6.80*E*−05	G	A	−0.088	0.022	0.369	62.2	RAB4A; SPHAR
3	170075515	170151885	SKIL	1.12*E*−04	67	rs13101192	3.80*E*−05	G	C	0.074	0.018	0.934	83.4	CLDN11
6	35911292	36200567	MAPK13	1.22*E*−04	72	rs7752459	8.10*E*−05	C	T	−0.093	0.024	0.949	89.8	MAPK14; SLC26A8; BRPF3
12	38710556	39299420	CPNE8	1.44*E*−04	269	rs864324	6.20*E*−05	A	G	−0.053	0.013	0.977	53.6	ALG10B
1	955502	1051736	AGRN	1.71*E*−04	19	rs7545952	1.68*E*−04	A	G	−0.177	0.047	0.303	94.3	C1orf159
8	124084919	124222318	WDR67	2.08*E*−04	200	rs2385165	3.80*E*−05	A	C	0.061	0.015	1.000	75.2	FAM93A
6	131466460	131604673	AKAP7	3.22*E*−04	181	rs3777474	8.10*E*−05	A	G	0.054	0.014	0.975	63.7	AKAP7
2	228549925	228682280	CCL20	3.71*E*−04	81	rs13385901	4.00*E*−06	C	A	0.096	0.021	0.811	84.0	SLC19A3
3	119885878	119962945	GPR156	4.16*E*−04	169	rs4676822	1.07*E*−04	T	G	−0.101	0.026	0.963	92.9	
5	140603077	140892546	PCDHB15	4.61*E*−04	89	rs10044936	1.20*E*−05	C	T	−0.151	0.035	0.860	95.6	PCDHB14; SLC25A2; TAF7; PCDHGA[a]; PCDHGB[a]
2	216807313	216967494	PECR	5.90*E*−04	113	rs934154	4.20*E*−05	T	C	0.058	0.014	0.978	69.0	MREG; TMEM169
3	57994126	58157977	FLNB	7.96*E*−04	287	rs13077017	1.00*E*−06	C	T	−0.073	0.015	0.933	71.0	
7	82993221	83278324	SEMA3E	9.90*E*−04	425	rs2713189	1.39*E*−04	C	T	−0.050	0.013	0.996	53.9	
14-Item case/control for disordered eating behaviors														
1	152184557	152386728	FLG2	"0" (next lowest is 3*E*−6)	74	rs3120667	1.66*E*−06	A	G	−0.118	0.025	0.956	84.5	FLG; CRNN; HRNR
10	91061705	91180753	IFIT3	1.31*E*−04	74	rs627524	1.83*E*−05	C	A	−0.076	0.018	0.998	47.8	IFIT1L; IFIT1; IFIT5; IFIT2
5	65222383	65376850	ERBB2IP	1.42*E*−04	134	rs251614	5.70*E*−05	C	G	−0.104	0.026	0.852	85.2	ERBB2IP
5	140588290	140683612	PCDHB15	2.15*E*−04	89	rs2910330	5.07*E*−04	G	T	−0.081	0.023	0.990	83.6	PCDHB12; PCDHB13; PCDHB14; SCL25A2
2	234160216	234255701	ATG16L1	2.65*E*−04	128	rs6759896	1.70*E*−04	A	G	0.070	0.019	0.863	58.4	SAG
3	170075515	170151885	CLDN11	2.81*E*−04	81	rs4292231	2.45*E*−04	G	C	0.092	0.025	0.791	80.4	SKIL
4	699572	1381837	PCGF3	3.73*E*−04	93	rs6816483	7.00*E*−04	C	T	−0.064	0.019	0.965	68.5	CPLX1; SPON2; KIAA1530
10	102672325	102800998	LZTS2	3.81*E*−04	63	rs807029	1.86*E*−04	C	T	0.077	0.021	0.869	72.5	FAM178A; SEMA4G; MRPL43; C10orf2; PDZD7; SFXN3
11	69924407	70053486	TMEM16A	4.08*E*−04	210	rs2509175	9.80*E*−05	T	A	0.106	0.027	0.586	77.8	FADD
19	18045904	18124911	KCNN1	4.53*E*−04	76	rs4808105	3.67*E*−04	C	T	−0.065	0.018	0.980	67.4	CCDC124; ARRDC2
4	156587877	156728056	GUCY1B3	5.09*E*−04	139	rs17033585	2.52*E*−04	G	A	0.128	0.035	0.366	78.4	GUCY1A3
16	27471933	28074830	GSG1L	5.18*E*−04	312	rs1645336	1.24*E*−03	T	C	−0.068	0.021	0.998	75.7	GTF3C1; KIAA0556
1	955502	1051736	C1orf159	5.70*E*−04	31	rs6689308	5.62*E*−04	A	G	−0.087	0.025	0.885	83.9	AGRN
17	3827168	4046253	ATP2A3	5.97*E*−04	85	rs9914203	2.96*E*−04	G	A	0.219	0.060	0.458	95.2	ZZEF1
19	5455425	5456867	ZNRF4	7.27*E*−04	69	rs529515	3.76*E*−03	A	G	0.074	0.025	0.469	52.3	ZNRF4
4	69681728	69696620	UGT2B10	9.71*E*−04	62	rs9329034	1.29*E*−03	T	C	0.096	0.030	0.827	89.6	UGT2B10

Obtained using VEGAS software based on 1000 Genomes per-SNP *p*-values. Because of software limitation, this only considers SNPs found in HapMap Phase II, and was not run for the X chromosome. Genes have been merged into one entry and shown for the lowest *p*-value where multiple genes in the same LD block are associated. The number of underlying SNPs (or range of numbers, if multiple genes) is shown. In most cases, there are many other genes within ∼200 kbp. Figure 3 includes plots of per-SNP association for entries highlighted in bold [reference SNP for the plot may differ from the one quoted here].

[a] Many genes in that family.

reached genome-wide significance for common variants within 1 KGP imputed data of $p < 10^{-8}$. Regional association plots for these suggestive signals are shown in **Figure 3**. The power associated with our strongest SNPs (at $p < 10^{-5}$) was $R^2 < 0.5$ for 9, $R^2 < 0.6$ for 15, and $R^2 < 0.7$ for 21, indicating that they were well imputed.

Attempted Replication of Results from the Previous GWAS Studies

We examined our results for the regions containing SNPs and CNV regions reported as associated with AN by Wang et al.,[11] and the other previously reported associated SNPs reported earlier[12,32] and in a Japanese population,[10] replication of which was tested in Wang et al. The *p*-values for the relevant SNPs in our data are reported in **Table 4**, along with MAF from our imputed data and the referenced papers (all for Europeans by Wang et al.[11] and for Japanese by Nakabayashi et al.[10]) for rs2048332. Our frequencies are consistent with the range between case and control frequencies for Wang et al.[11] (suggesting good imputation) but we fail to replicate (in any of our phenotypes) their associated SNPs for AN or those reported earlier.[10,12,32] We do find a nominally significant association ($p \sim .01$) in both the BN spectrum and 14-item disordered eating behavior variable for rs906281, which Wang et al.[11] investigated as a proxy for rs2048332 which was itself reported by Nakabayashi et al.[10] However, this is significant only in terms of the limited number of tests shown in **Table 4**, and is for a different population.

Discussion

This study represents only the fourth published GWAS for eating disorders-related phenotypes and extends the literature by examining four broad eating disorder phenotypes assessed by self-report—AN spectrum, BN spectrum, purging via substances, and disordered eating behaviors. A number of suggestive signals were identified, although none reached genome-wide significance at the level of $p < 10^{-8}$. The strongest evidence of association was observed at rs145241704, rs62090893, and rs561 56506 for the AN spectrum phenotype, rs1445130 for the BN spectrum phenotype, rs138206701 for the purging phenotype, and rs7322916 for the disordered eating behaviors phenotype.

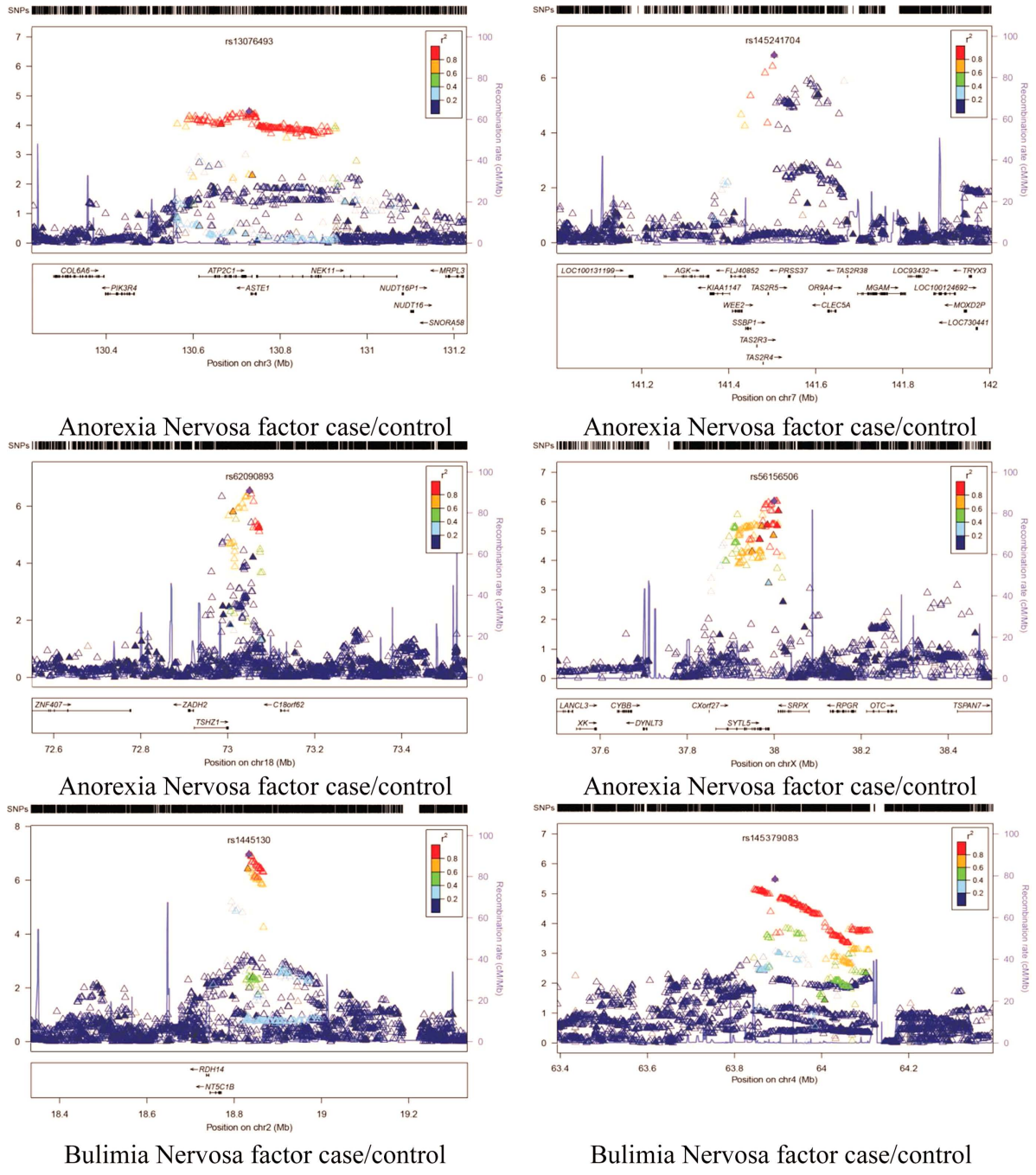
The strongest signal for our AN spectrum variable is located in a gene-rich region on chromosome 7 (141.5Mb). Within this region are a number of promising positional candidates. The peak variant in this region, rs145241704, is located within the mRNA *DQ571874*, which has previously been identified as a Piwi-interacting RNA playing a role in gamete development. However, the LD block within this region includes a number of taste receptor genes including *TAS2R3*, *TAS2R4*, and *TAS2R5*, which encode bitter taste receptors. Such receptors have previously been shown to influence perception and eating behaviors with respect to certain foods. Also within this region is *CLEC5A*, which is a carbohydrate-binding protein domain that has a diverse range of functions including cell–cell adhesion, immune response to pathogens, and apoptosis. The next strongest signal, which peaked at rs62090893, encompasses the *TSHZ1* gene. Notably, in a recent study examining changes in gene expression in response to bariatric surgery in a sample of patients with Type 2 diabetes,[33] changes in expression of *TSHZ1* were correlated with changes in weight, fasting plasma glucose, and glycosylated hemoglobin.

The strongest result for the BN spectrum phenotype was located in an intergenic region centered around rs1445130 on chromosome 2. Recent results from the ENCODE consortium have shown enrichment of the *H3K27Ac* histone marks within this region, suggesting that there may be an active regulatory region nearby. The closest gene, NT5C1B, plays a role in the production of adenosine, which plays an important role in biochemical processes, such as energy transfer.

Consistent with research in other areas of psychiatric genetics prior to accumulation of large sample sizes, there was no meaningful replication between previous genome-wide studies of AN and our current results. If eating disorders follow the same scientific trajectory of other medical and psychiatric disorders, which is increased replication and clarity with increasingly large sample sizes[34]—and there are not theoretical reasons why they should not—then we would expect more concrete results as we combine samples into meta-analyses.

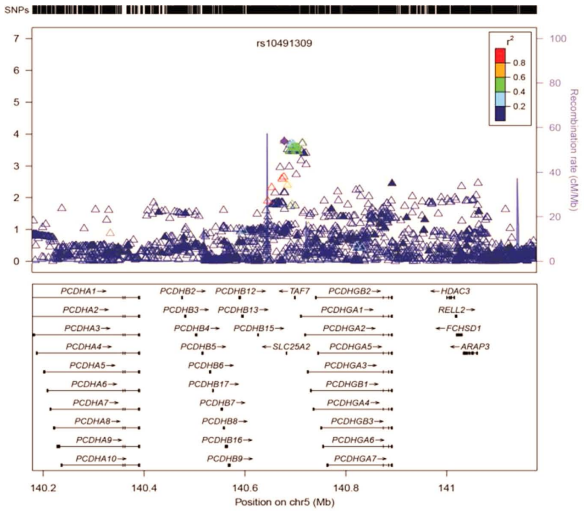
This study has a number of limitations; first, we used self-report data that are not directly reflective of the diagnostic criteria for eating disorders. Although our data cluster in recognizable eating disorder syndromes,[24] the phenotypes represent rather a blunt instrument for identifying specific eating disorders. Second, as with other studies of psychiatric illness that have used population-based samples, the analyses are underpowered. Third, there are only 45 persons who would qualify for a diagnosis of BN or AN in our genotyped sample,[35]

FIGURE 3. Association peak regional plots of per-SNP association *p*-values for (1) the most highly associated but plausible association peaks for each phenotype (i.e., containing a group of adjoining associated SNPs in high LD); (2) additional associated genes (highlighted in bold in Tables 2 and 3). Obtained for Build 37/hg19 coordinates using v1.1 of LocusZoom, with LD data for 1000 Genomes release 20101123 (http://genome.sph.umich.edu/wiki/LocusZoom_Standalone). Shown with recombination rate (underlying blue graph) and annotated with names and positions of known genes if any (box below each plot). Symbols for SNPs are as follows: filled diamond for most associated SNP (as named); filled triangle if genotyped or open triangle if purely imputed. Coloring indicates LD with the named SNP (gray = LD unknown) based on genotypes from 1000 Genomes release "20101123." The phenotype name is labeled below each panel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

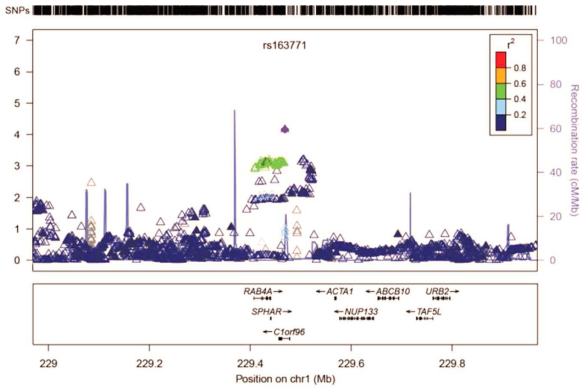


so our ability to contribute cases to larger case–control samples is limited. However, GWAS now exist that are not focused on diagnosis but on eating disorder-related symptoms and behaviors.[12] As GWAS meta-analysis by definition requires the availability of a number of samples, and a review of the genetic architecture of psychiatric disorders shows that sample size is of greater importance

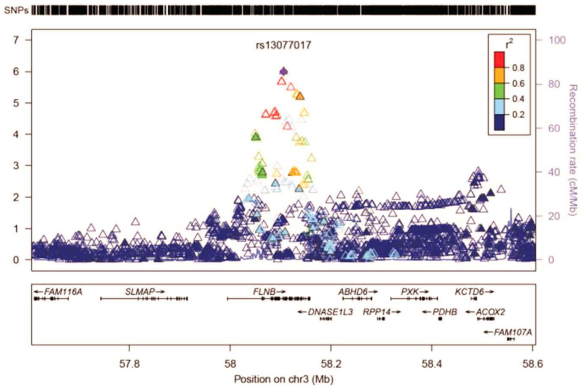
FIGURE 3. (Continued).



Bulimia Nervosa factor case/control



Purging factor case/control



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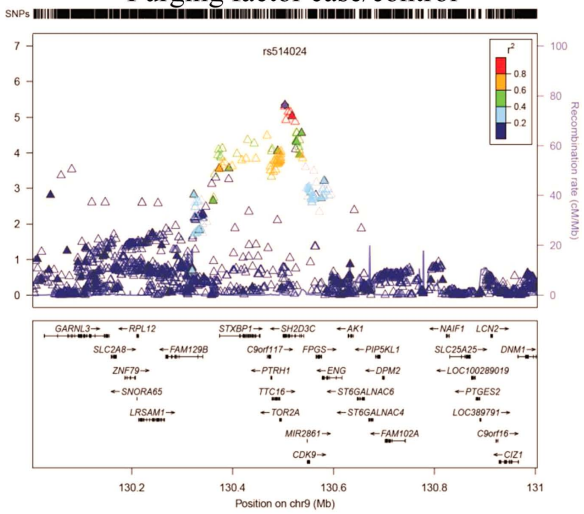
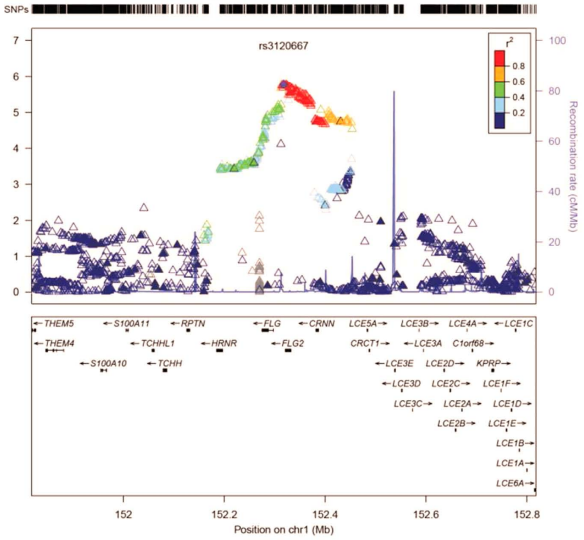
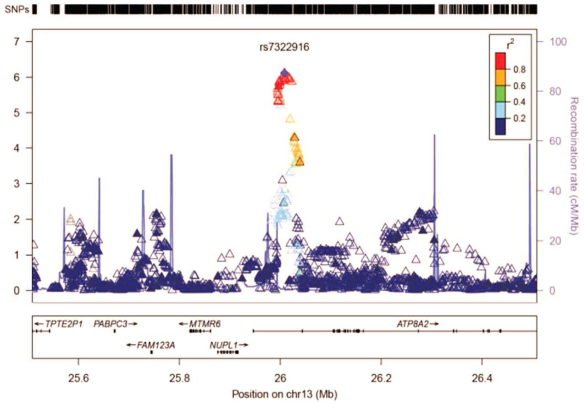


Purging factor case/control



14-item case/control



14-item case/control

TABLE 4. Replication of previous studies: Per-SNP association *p*-values for SNPs reported associated with AN in previous literature (as labeled) where available in our analysis

	p-Values for Anorexia Nervosa Spectrum Factor Case/Control		*p*-Values for Bulimia Nervosa Spectrum Case/Control		*p*-Values for Tablet Purging Factor Case/Control		*p*-Values for 14-Item Case/Control Disordered Eating Behavior			
Reported SNP	Observed Genotypes	1000G Dosage	Observed Genotypes	1000G Dosage	Observed Genotypes	1000G Dosage	Observed Genotypes	1000G Dosage	Imputed MAF (%)—Here	MAF (%) in Referenced Paper (AN Case; Control)
SNPs associated in Table 1 of Wang et al.[6]										
rs6959888	.038	.035	.950	.846	.300	.207	.330	.243	11.8	15; 11
rs17725255	.074	.051	.104	.100	.440	.669	.990	.586	12.5	14; 11
rs10494067	.870	.852	.650	.658	.062	.061	.260	.265	6.1	3; 6
rs2383378	.460	.809	.660	.621	.810	.100	.780	.144	37.2	35; 41
rs410644	.730	.708	.200	.180	.460	.408	.640	.562	45.7	41; 47
rs4479806	.320	.346	.670	.687	.250	.305	.450	.538	8.7	6; 10
rs957788	.800	.805	.250	.250	.240	.334	.580	.643	33.2	37; 31
rs830998	.170	.147	.137	.975	.420	.348	.810	.372	20.7	23; 19
rs6782029	.810	.887	.570	.530	.570	.595	.470	.518	23.2	19; 24
rs512089	.870	.844	.190	.234	1.000	.897	.490	.610	25.6	28; 24
rs3808986	.400	.386	.860	.844	.510	.503	.980	.994	6.9	5; 8
SNPs associated in Brown et al.[32]										
rs569356		.841		.511		.999		.683	13.3	?
rs856510		.551		.785		.564		.591	31.9	?
SNPs associated (in Japanese) in Nakabayashi et al.[10]										
rs2048332		.696		.262		.711		.824	31.1	?
SNPs which Wang et al.[6] investigated (as proxies for SNPs associated by Brown et al.)										
rs533123	.160	.993	.270	.903	.380	.905	.090	.857	18.9	21.7; 18.6
rs7532266	.640	.667	.660	.670	.830	.799	.880	.843	31.2	31.1; 32.0
SNPs which Wang et al.[6] investigated (as proxies for markers associated in Nakabayashi et al.)										
rs6604568	.490	.517	.260	.275	.750	.760	.790	.783	27.9	28.0; 29.7
rs906281	.099	.111	.011	.010	.035	.036	.010	.010	22.1	?
Body dissatisfaction (BD) phenotype SNPs (with $p < 10^{-5}$) from Table III in Boraska et al.[12]										EAF from paper (%)
rs6894268	.74	.601	.41	.599	.27	.994	.74	.316	31.9	35.4
Bulimia phenotype SNPs (with $p < 10^{-5}$) from Table III in Boraska et al.[12]										
rs7624327	.21	.205	.65	.635	.54	.567	.71	.760	10.9	9.8
"OCPD" phenotype SNPs (with $p < 10^{-5}$) from Table III in Boraska et al.[12]										
rs7690467	.91	.931	.016	.017	.093	.094	.54	.532	29.2	28.5
rs1898111	.87	.850	.0046	.0043	.016	.016	.0076	.008	17.0	16.3
rs10519201	.91	.927	.38	.380	.13	.125	.91	.921	13.7	13.2
rs1557305	.56	.563	.34	.351	.78	.835	.94	.824	36.9	37.2
Weight fluctuation (WF) phenotype SNPs (with $p < 10^{-5}$) from Table III in Boraska et al.[12]										
rs4853643	.19	0.198	.42	.421	.59	.577	.43	.457	18.4	17.8
rs218361	.19	0.207	.56	.584	.68	.797	.67	.633	41.2	42.9

rs674386 (from Brown et al.) was not available, observed or imputed. Imputed dosages cover all ~2,557 phenotyped individuals. Observed genotypes cover ~1,217 phenotyped individuals (rs17725255, 2383378, and rs830998); ~1,497 (rs533123); otherwise ~2,550 (less minor dropout for each phenotype).

than heritability with respect to the identification of specific loci,[21] our analyses should make a useful contribution toward improving the power to identify genetic variants influencing symptoms and behaviors related to eating disorders through the conduct of meta- and mega-analyses with other such GWAS.

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