Article

Genome-wide study suggests an association of the enhancer rs10419198 for *PRR12* gene with disordered eating behavior in the Mexican population

José Jaime Martínez-Magaña[1], Sandra Hernandez[2], Ana Rosa Garcia[3], Valeria Cardoso-Barajas[4], Emmanuel Sarmiento[5], Beatriz Camarena[6], Alejandro Caballero[7], Laura Gonzalez[8], Jorge Ameth Villatoro-Velazquez[9], Maria Elena Medina-Mora[10], Marycarmen Bustos-Gamiño[11], Clara Fleiz-Bautista[12], Carlos Alfonso Tovilla-Zarate[13], Isela Esther Juárez-Rojop[14], Humberto Nicolini[15,*], Alma Delia Genis-Mendoza[16,*]

1 Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, CDMX, México; jimy.10.06@gmail.com
2 Laboratorio de Farmacogenética, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; sanher90@hotmail.com
3 Unidad de Investigación, Hospital Psiquiátrico Infantil Juan N Navarro, CDMX, México; anarosagarciab@gmail.com
4 Unidad de Investigación, Hospital Psiquiátrico Infantil Juan N Navarro, CDMX, México; morganakvm@hotmail.com
5 Unidad de Investigación, Hospital Psiquiátrico Infantil Juan N Navarro, CDMX, México; emmanuel.sarmiento@salud.gob.mx
6 Laboratorio de Farmacogenética, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; camare@imp.edu.mx
7 Unidad de trastornos alimenticios, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; alexcarom@hotmail.com
8 Unidad de trastornos alimenticios, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; macias@imp.edu.mx
9 Unidad de análisis de datos y encuestas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; ameth@imp.edu.mx
10 Unidad de análisis de datos y encuestas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; metmmora@gmail.com
11 Unidad de análisis de datos y encuestas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; naomi_gam@hotmail.com
12 Unidad de análisis de datos y encuestas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, CDMX, México; clarafleiz@yahoo.com.mx
13 División Académica Multidisciplinaria de Comalcalco, Universidad Juárez Autónoma de Tabasco, Comalcalco, México; alfonso_tovillaz@yahoo.com.mx
14 División de Ciencias de la Salud, Universidad Juárez Autónoma de Tabasco, Villahermosa, México; iselajuarezrojop@hotmail.com
15 Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, CDMX, México; hnicolini@inmegen.gob.mx
16 Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, CDMX, México; adgenis@inmegen.gob.mx

* Correspondence: HN hnicolini@inmegen.gob.mx and ADGM adgenis@inmegen.gob.mx; Tel.: (55 5350 1900, ext. 1917 and 1916)

Abstract: Eating disorders (ED) are characterized by alterations in eating behavior. The genetic factors shared between ED diagnoses have been underexplored. The present study aimed to perform a genome-wide association study on individuals with disordered eating behaviors in the Mexican population, blood methylation quantitative trait loci (blood-meQTL) analysis, and *in silico* function prediction by different algorithms. The analysis included a total of 1803 individuals. Genome-wide association study and blood-meQTL analysis were performed by logistic and linear regression. *In silico* functional variant prediction, phenome-wide, and transcriptome-wide association studies by different algorithms were analyzed. In the genome-wide association study, we identified 44 single-nucleotide polymorphisms (SNP) associated at a nominal value and 7 blood-meQTL at a genome-wide umbral. The SNPs were enriched in genome-wide associations of the metabolic and immunologic domains. In the in silico analysis, the SNP rs10419198 located on an

enhancer mark could change the expression of *PRR12* on blood, adipocytes, and brain areas that regulate food intake. The present study supports the previous associations of genetic variation in the metabolic domain with ED.

Keywords: feeding and eating disorder; genome-wide association study; methylation quantitative trait loci

1. Introduction

Eating disorders (ED) have serious consequences on physical and mental health [1–3]. Disordered eating is the presence of some behaviors like fasting, vomiting, binge eating, and food intake restriction [4,5]. Anorexia nervosa, bulimia nervosa, and binge-eating disorder are the three main ED diagnoses [6]. Individuals diagnosed with ED have different patterns of disordered eating and this could change over time [7–9]. Even when the diagnosis criteria for different ED are well established [6], affected individuals may have a phenomenon of crossover diagnosis [10–12]. The diagnosis crossover is proposed to be based on the close relationship between the ED criteria and the overlapping of symptoms [8]. It also has been proposed that such crossover could be an escalation mechanism, mainly in individuals with BED [13].

Since different biological and environmental risk factors interact [14], unraveling the etiology of ED has shown to be highly complex. Also, it is well known that ED may share risk factors like gender, dieting, or weight concerns, most of which take place early in life or during adolescence [15].

The genetic basis that underlies many psychiatric disorders has been extensively explored in the last decade and its analysis at the genome-wide level has shown that these disorders share genetic factors [16,17]. Genome-wide association studies research has been in individuals with AN [18–22]. It has been suggested that AN has a genetic correlation with other psychiatric phenotypes or metabolic traits [18,22]. Nevertheless, the genetic factors shared between ED diagnoses are less explored. The present work aimed to explore a genome-wide analysis, blood methylation quantitative loci analysis, and *in silico* prediction of function, in individuals with disordered eating patterns in the Mexican population, to explore genetic factors shared between these disorders.

2. Materials and Methods

2.1. Sample population

The study included a total of 1803 individuals of Mexican descent, taken from three different samples: an adolescent clinical subsample taken from the Mexican Genomic Database for Cross-Disorder Research (n = 168, MeDaCrosR) [23,24], a clinical sample recruited from the ED Unit of the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (n = 166, INPRFM), and an epidemiological subsample taken from the Mexican Genomic Database for Addiction Research (n = 1,469, MxGDAR) [25,26] (Table 1).

Table 1. Overview of the characteristics of the samples.

Characteristic	MeDaCrosR (n = 168)	INPRFM (n = 166)	MxGDAR (n = 1,469)
Age, mean (s.d)	13.96 (1.94)	19.32 (4.82)	35.86 (15.77)
Gender			
Male, n(%)	42 (0.25)	16 (9.64)	388 (26.41)
Female, n%()	126 (0.75)	150 (90.36)	1081 (73.59)

Adolescents from the MeDaCrosR were recruited from the Hospital Psiquiátrico Infantil Juan N Navarro (HPIJNN), from external consultation. Eating patterns in

MeDaCrosR adolescents were evaluated by children's specialized psychiatrists through the Eating Attitude Test 26 (EAT26) [27,28] and the Questionnaire on Eating and Weight Patterns Revised (QWEPR) in Spanish [29]. The adult sample from the INPRFM was diagnosed according to DSM-IV-TR criteria for ED using the Structured Clinical Interview for Mental Disorders v.2.0. (SCID-I) [30] and evaluated with the EDI-2 for psychological patterns [27,28]. The groups from MeDaCrosR and INPRFM were considered as cases of disordered eating (n = 333). Meanwhile, the individuals from the MxGDAR were considered population-based controls (n= 1802). Individuals from the MxGDAR were evaluated with the screening section of the Diagnostic Interview for Psychosis and Affective Disorders [26,31–34]. The study was performed based in the Helsinki declaration, and was revised by the ethic and investigation committees of the Instituto Nacional de Medicina Genómica (Approval number CEI/2018/60), Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (Approval number: DGC-279-2008), and the Hospital Psiquiátrico Infantil Juan N Navarro (Approval number II3/01/0913). Every individual fulfilled and signed an informed assent (adolescents) and/or consent (parents/adults).

2.2. Microarray analysis

DNA from blood and buccal epithelial samples was extracted with a modified method of salting-out, implemented in the commercial kit Gentra Puregene (Qiagen, USA). According to the manufacturer's protocol, genotyping was performed in the Instituto Nacional de Medicina Genómica with the commercial Infinium PsychArray Beadchip (Illumina, USA). Fluorescent intensities were measured with the iScan (Illumina, USA), transformed to genotypes with the GenomeStudio (Illumina, USA), and converted to Plink format files. Quality control of genotypes was performed in Plink software [35,36], based on previously published protocols, briefly, the following criteria were considered: variant calling greater than 95%, a minor allele frequency (MAF) greater than 5%, a Hardy-Weinberg equilibrium chi-square test p-value greater than 1e-5, and variants A/T or G/C (to avoid the flip strand effect). Individuals with a genotype call rate of less than 95% were excluded. To correct for cryptic relationships, all individual pairs with an identity-by-state value greater than 1.6 were marked, and the individual with the lowest genotype call rate was excluded.

2.3. Statistical analysis

2.3.1. Population stratification

Population stratification was evaluated with a principal components analysis using previously reported algorithms and the *PC-AiR* package [37]. The Human Genome Diversity Project (HGDP) was used as a reference [38]. Linkage disequilibrium pruning (LD pruning) was carried out, using the following parameters: a window size of 50Kb, a step of 2, and a variance inflation factor of 5 implemented in Plink.

2.3.2. Genome-wide genotype-phenotype associations

The genetic associations were carried out through multiple logistic regressions, adjusted for age, sex, and ten components of global ancestry as covariables. A p-value of 5.00e-05 was considered nominally associated and a p-value of 5.00e-08 was considered statistically significant on the genome-wide level. The logistic regressions were carried out in Plink. After statistical contrasts, all the variants with a MAF lower than 5.0% in cases or controls were removed. Logistic regressions were carried out in Plink.

2.3.3. Functional prediction

An in silico functional annotation was also carried out of the associated SNPs using Variant Effect Predictor (VEP) [39]. A phenome-wide association study was performed in the GWAS atlas of the associated SNPs, a considered signal of a p-value < 5e-08 [40]. Pathway analysis was carried out with the online ComPath tool [41]. A search in the GWAS atlas of the associated SNPs was performed for associations with different

phenotypes. In silico multi-tissue, expression quantitative trait loci analysis (eQTL) was performed using the GTEx portal [42,43].

2.3.4. Methylation quantitative trait loci analysis

The possible impact of the associated SNPs on blood DNA methylation levels was assessed by calculating methylation quantitative trait loci (blood-meQTL) on individuals diagnosed with eating disorders of Mexican ascendence from a previously published database [44]. The DNA methylation levels were determined using Illumina MethylationEPIC BeadChips (Illumina, USA). A calculation of *trans*- and *cis*-meQTL was performed with KING software [45], and p-value < 5.00e−8 was considered genome-wide statistically significant. The associated SNPs with eQTL and blood-meQTL effect were searched in the regulomeDB for enhancer or promoter marks [46].

3. Results

In the genotype-phenotype associations, no genome-wide associations were found, nevertheless, 44 single-nucleotide polymorphisms (SNP) were associated at a nominal level (p-value < 5e-05) (Table 2). The SNPs were distributed in 29 cytogenetic bands and 19 coding regions. The protein-coding genes with SNPs associated with disordered eating were enriched in the PI3K-Akt signaling pathway (hsa04151, adjusted p-value = 0.0499, *FTL3LG* and *TSC2*), vascular muscle contraction (hsa04270, adjusted p-value = 0.0494, *KCNMA1* and *PRKCE*), and cGMP – PKG signaling pathway (hsa04022, adjusted p-value = 0.0494, *KCNMA1* and *PRKCE*). Of the total 44 SNPs, 22 were intronic and 2 were missense variants. The missense variants were the *SRMM4* p.Ser243Asn and *FLT3LG* p.Phe177Leu.

Table 2. Associated SNPs to disordered eating in Mexican population

SNP	Band	Position	A1/A2	MAF Cases	MAF Controls	OR	L95	U95	P-value	Gene	Effect
rs17030129	1p36.31	1:7059150	A/G	0.3787	0.3145	1.685	1.325	2.141	2.03e-05	*CAMTA1*	Intron
rs11120813		1:7062993	A/G	0.4414	0.3720	1.646	1.306	2.075	2.45e-05		
rs6690584		1:7078434	G/T	0.4401	0.3645	1.718	1.359	2.170	5.87e-05		
rs7521204	1p36.13	1:19138295	T/C	0.5329	0.4193	1.672	1.330	2.100	1.03e-05	*Intergenic*	-
rs12024738	1q31.1	1:190694813	A/G	0.5285	0.4238	1.577	1.267	1.964	4.65e-05	*LINC01720*	Intron
rs4626924	1q42.3	1:234909298	C/T	0.2260	0.2862	0.5861	0.4536	0.7573	4.38e-05	*LOC107985364*	
rs867286	2p21	2:45982030	A/G	0.4505	0.3821	1.655	1.321	2.074	1.18e-05	*PRKCE*	Intron
rs11677196	2p12	2:75830221	A/G	0.2949	0.3754	0.5947	0.4688	0.7546	1.83e-05	*Intergenic*	-
rs3205060	2q31.1	2:175425346	G/A	0.4249	0.3410	1.657	1.318	2.084	1.57e-05	*WIPF1*	3′-UTR
rs7569439	2q35	2:220590633	C/T	0.3091	0.3712	0.57	0.4472	0.7266	5.67e-06	*Intergenic*	-
rs35542515		4:161798045	A/C	0.2733	0.2063	1.93	1.472	2.529	1.91e-06		
rs2748991	6p12.2	6:52596516	C/T	0.4234	0.3099	1.662	1.303	2.118	4.16e-05		
rs3801220	7p14.1	7:42247876	G/A	0.5494	0.4506	1.729	1.379	2.167	2.11e-06	*GLI3*	Intron
rs3801232		7:42253313	T/C	0.5284	0.4282	1.778	1.412	2.238	9.70e-07		
rs4724100		7:42264679	C/T	0.5254	0.4316	1.726	1.371	2.174	3.50e-06		
rs4507768	8q13.3	8:70642018	A/G	0.1272	0.1703	0.5027	0.3635	0.6952	3.23e-05	*SLCO5A1*	Intron

rs10114881	9q21.13	9:76676071	T/C	0.5254	0.4298	1.628	1.293	2.049	3.34e-05	*Intergenic*	-
rs12241514	10p12.31	10:21602923	A/G	0.1257	0.2088	0.4525	0.3293	0.6219	1.02e-06		
rs1865020	10q22.3	10:78688976	C/T	0.4566	0.3764	1.634	1.301	2.052	2.45e-05	*KCNMA1*	Intron
rs7918074	10q26.3	10:134277154	A/G	0.2380	0.1547	1.922	1.448	2.551	6.20e-06	*LOC105378569*	
rs10870311		10:134290526	A/C	0.3228	0.2279	1.751	1.347	2.275	2.77e-05	*Intergenic*	-
rs10772471	12p13.2	12:116003604	A/G	0.3802	0.2754	1.66	1.301	2.117	4.58e-05	*LOC440084*	Intron
rs7297606	12q24.3	12:119568596	A/G	0.1886	0.1605	1.918	1.415	2.599	2.66e-05	*SRRM4*	Missense (p.Ser243Asn)
rs4075945		12:119569784	T/C	0.1886	0.1609	1.915	1.413	2.599	2.78e-05		Intron
rs12809631		12:131045190	A/C	0.1467	0.1954	0.5341	0.3992	0.7146	2.41e-05	*RIMBP2*	
rs2144067	14q32.31	14:101952406	T/C	0.2156	0.2330	0.5547	0.4198	0.7330	3.42e-05	*Intergenic*	-
rs1007904		14:101955905	A/G	0.2380	0.2589	0.5720	0.4370	0.7488	4.80e-05		
rs7163468	15q12	15:26587077	T/C	0.2036	0.1243	1.915	1.399	2.621	4.96e-05		
rs3922665		15:26590830	G/A	0.2425	0.1552	1.885	1.413	2.514	1.60e-05		
rs8041059	15q21.3	15:58743709	T/C	0.2710	0.1999	1.732	1.329	2.256	4.72e-05	*LIPC*	Intron
rs11073665	15q25.3	15:87295120	G/A	0.4027	0.3281	1.626	1.295	2.041	2.78e-05	*AGBL1*	
rs17135764	16p13.3	16:2111779	T/C	0.2440	0.3144	0.5455	0.4249	0.7003	1.99e-06	*TSC2*	Intron
rs11862729	16p13.12	16:14146098	G/A	0.2395	0.1789	1.809	1.364	2.4000	3.87e-05	*Intergenic*	-
rs12454763	18q12.3	18:42434615	A/G	0.4102	0.3341	1.673	1.328	2.108	1.26e-05	*SETBP1*	Intron
rs991014		18:42439886	A/G	0.4096	0.3349	1.705	1.350	2.154	7.49e-06		
rs1042122	19q13.3	19:49989424	C/T	0.2769	0.3567	0.5677	0.4447	0.7246	5.46e-06	*FLT3LG*	Missense (p.Phe177Leu)
rs10419198		19:50038017	T/C	0.3084	0.3833	0.6054	0.4798	0.7638	4.85e-05	*RCN3*	Intron
rs6074170	20p12.2	20:10671078	A/G	0.4162	0.3501	1.5940	1.2730	1.9970	4.85e-05	*Intergenic*	-
rs4813048		20:11169603	T/C	0.2575	0.1821	1.8440	1.3870	2.4520	2.55e-05		
rs6043684	20p12.1	20:16023836	A/C	0.4096	0.3066	1.6330	1.2980	2.0560	2.88e-05	*MACROD2*	Intron

rs6104082	20q13.12	20:43897362	C/T	0.3423	0.2827	1.6750	1.3060	2.1470	4.70e-05	*LOC105372630*	
rs2824006	21q21.1	21:18099779	C/T	0.4386	0.3584	1.5930	1.2760	1.9900	4.00e-05	*Intergenic*	-
rs2824065		21:18187408	C/T	0.3997	0.2968	1.6910	1.3380	2.1370	1.09e05		
rs71330155		21:22059184	A/C	0.1587	0.2234	0.5276	0.3922	0.7098	2.38e-05		

Note: SNP = singel-nucleotine polimorfism , Band = cytogeneitc band, Position = genomic coordiantes, A1/A2 = minor allele/major allele frequency, MAF = minor allele frequency, OR = odds ratio, L95 = low 95% confidence interval, U95 = upper 95% confidence interval, Effect = in-silico variant effect prediction

In the PheWAS we identified the immunological (rs4626924 andrs10419198) and metabolic (rs3205060, rs8041059, and rs10419198) domain with SNPs associated. The SNPs associated with the immunological domains were both intronic one located in the coding region of *LOC107985364* and the other in *RCN3*. In the metabolic domain, the rs8041059 located in the intron of *LIPC* has been associated with 33 different lipidic traits.

The blood-meQTLs analysis showed 7 SNPs associated with changes in the methylation levels of 5 CpG sites (Table 3). The CpG sites were located in 4 genes, including the rs10419198 associated with changes in the body of the *PRR12* gene.

Table 3. Blood methylation quantitative loci (blood-meQTL)

SNP	CpG	Gene	Location	Beta	SE	P-value
rs12024738	cg12412036	*LOC440704*	TSS200	-0.0869	0.0114	2.4216e-14
rs12245880	cg09420738			0.1041	0.0155	1.7351e-11
rs12454763	cg12522870	*SETBP1*	Body	-0.0775	0.0109	1.6124e-12
rs991014				-0.0775	0.0109	1.6124e-12
rs10419198	cg06378142	*PRR12*	Body	-0.3768	0.0502	6.2212e-14
rs2233903	cg15921833	*SEMG1*	TSS1500	0.2124	0.0153	5.1650e-44
rs6104082				0.1895	0.0195	2.3470e-22

Note. SNP = ingle-nulceotide polymorphism, CpG = cytocine to guaninces nulceotides, SE = standard error

The multi-tissue eQTL analysis, in the GTEx database, revealed that the rs10419198 had an eQTL effect on different tissues (frontal cortex, anterior cingulate cortex, cerebellum, putamen, thyroid, visceral adipose tissue, etc) (Figure 1). In the regulomeDB database, the rs10419198 showed a mark of enhancers in 51 different cell lines.

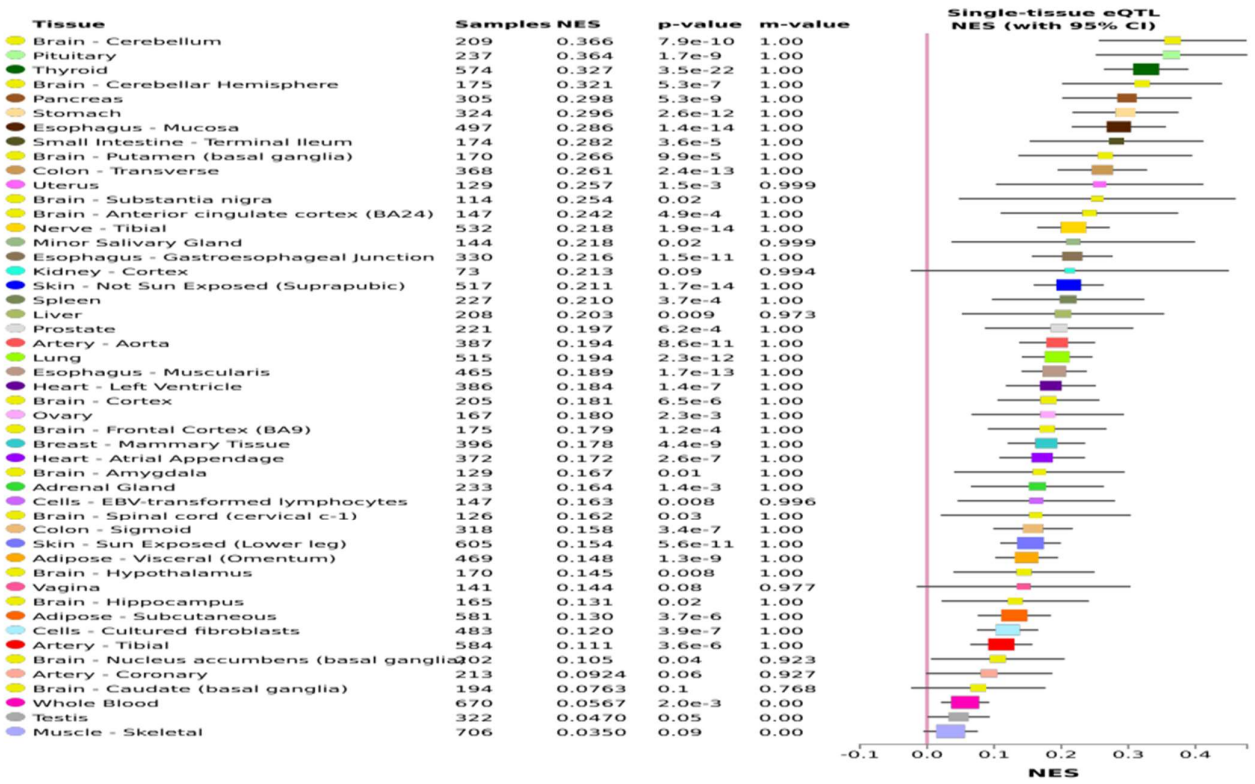

Figure 1. Multi-tissue eQTL results from the query to GTEx portal.

4. Discussion

Previous GWAS on ED have shown, mainly in AN, that genetic variants associated with this disorder could have a high impact on metabolic pathways [31–34]. The genetic association found in our study also supports this finding on individuals with disordered eating behavior. Three variants (rs3205060, rs8041059, and rs10419198) associated with disordered eating in our study had been previously associated at the genome-wide level with at least one metabolic trait. One associated variant was the rs8041059 which is found in the hepatic triglyceride lipase gene (*LIPC*) and is associated with differences in high-density lipoproteins (HDL), cholesterol, and triglyceride plasmatic levels [35,36]. *LIPC* catalyzes the hydrolysis of triglycerides and phospholipids found in circulating lipoproteins [37–39]. The effect of this variant is hypothesized to be suppressive and promoted by triglycerides concentration on the transcription factors acting on the promoter of *LIPC*, but the exact mechanism remains to be explored [40–42]. The association of this SNP could be important in the mechanism behind the reported increased levels of HDL on individuals diagnosed with AN [43,44].

The other variant with previous genome-wide signals in metabolic traits was rs10419198 [36]. The former variant is found in the intron of the *RCN3* gene. Our blood-meQTL and in silico analysis of multi-tissue eQTL showed that this variant modulates the expression of *PRR12* gene. *PRR12* is the proline-rich 12 protein, also known as KIAA1205. The exact cellular function of these proteins remains unknown but it is proposed that it has an important function on brain development. The function of this gene on the brain is supported by some studies, where individuals with loss-of-function or structural variation on this gene had clinical syndromes characterized by neurodevelopmental and eye abnormalities [45–47]. The main neurodevelopmental alterations found on the carriers of high impact variants on *PRR12* are autism, intellectual disability, and attention-

deficit/hyperactivity disorder (ADHD). ADHD is one of the most frequent comorbidities found in individuals with ED and the presence of this clinical entity could increase the symptoms of disordered eating [48–51]. Further analysis of the function of the gene *PRR12* could help us understand this high comorbidity.

Our study is one of the first to explore genetic associations at the genome-wide level with ED in the Mexican population. Nevertheless, some limitations could be stated, the main is the small sample size. This reduced sample size reduces our statistical power. Another limitation could be the lack of metabolic parameters measured in the sample. Also, that the population-based sample was not screened for disordered eating behavior. On the other hand, the integration of other sources of information like the in silico eQTL and blood-meQTL strengthens it.

5. Conclusions

The present study suggests an association of the rs10419198 enhancer variant of the PRR12 gene supporting previous reports that have found that disordered eating could imply genetic associations with metabolism.

6. Patents

No patents were generated in this study.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: title, Table S1: title, Video S1: title.

Author Contributions: Conceptualization, JJMM and ADGM; methodology, ADGM; software, JJMM; validation, SH, ADGM, and HN; formal analysis, JJMM; investigation, IEJR, CATZ, and AC; resources, CFB, MBG, MEMM, JAVV, LG, AC, BC, and ES; data curation, JJMM.; writing—original draft preparation, JJMM, and SH.; writing—review and editing, all authors; visualization, JJMM; supervision, HN; project administration, ADGM; funding acquisition, HN. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committees of the Psychiatric Hospital "Dr. Juan N. Navarro" (protocol code No. II3/01/0913; 11 October 2017), and National Institute of Genomic Medicine (INMEGEN) (protocol code No. 06/2018/I; June 2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author, which was omitted due to privacy and ethical issues.

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References

1. Berkman, N.D.; Lohr, K.N.; Bulik, C.M. Outcomes of Eating Disorders: A Systematic Review of the Literature. *Int. J. Eat. Disord.* **2007**, *40*, 293–309, doi:10.1002/eat.20369.
2. Smink, F.R.E.; van Hoeken, D.; Hoek, H.W. Epidemiology of Eating Disorders: Incidence, Prevalence and Mortality Rates. *Curr. Psychiatry Rep.* **2012**, *14*, 406–414, doi:10.1007/s11920-012-0282-y.
3. Santomauro, D.F.; Melen, S.; Mitchison, D.; Vos, T.; Whiteford, H.; Ferrari, A.J. The Hidden Burden of Eating Disorders: An Extension of Estimates from the Global Burden of Disease Study 2019. *Lancet Psychiatry* **2021**, *8*, 320–328, doi:10.1016/S2215-0366(21)00040-7.
4. Jalali-Farahani, S.; Chin, Y.S.; Mohd Nasir, M.T.; Amiri, P. Disordered Eating and Its Association with Overweight and Health-Related Quality of Life Among Adolescents in Selected High Schools of Tehran. *Child Psychiatry Hum. Dev.* **2015**, *46*, 485–492, doi:10.1007/s10578-014-0489-8.

5. Zeiler, M.; Waldherr, K.; Philipp, J.; Nitsch, M.; Dür, W.; Karwautz, A.; Wagner, G. Prevalence of Eating Disorder Risk and Associations with Health-Related Quality of Life: Results from a Large School-Based Population Screening: Prevalence of Eating Disorder Risk. *Eur. Eat. Disord. Rev.* **2016**, *24*, 9–18, doi:10.1002/erv.2368.
6. Vo, M.; Accurso, E.C.; Goldschmidt, A.B.; Le Grange, D. The Impact of DSM-5 on Eating Disorder Diagnoses. *Int. J. Eat. Disord.* **2017**, *50*, 578–581, doi:10.1002/eat.22628.
7. Pearson, C.M.; Miller, J.; Ackard, D.M.; Loth, K.A.; Wall, M.M.; Haynos, A.F.; Neumark-Sztainer, D. Stability and Change in Patterns of Eating Disorder Symptoms from Adolescence to Young Adulthood. *Int. J. Eat. Disord.* **2017**, *50*, 748–757, doi:10.1002/eat.22692.
8. Wu, X.Y.; Yin, W.Q.; Sun, H.W.; Yang, S.X.; Li, X.Y.; Liu, H.Q. The Association between Disordered Eating and Health-Related Quality of Life among Children and Adolescents: A Systematic Review of Population-Based Studies. *PLOS ONE* **2019**, *14*, e0222777, doi:10.1371/journal.pone.0222777.
9. Eichen, D.M.; Strong, D.R.; Rhee, K.E.; Rock, C.L.; Crow, S.J.; Epstein, L.H.; Wilfley, D.E.; Boutelle, K.N. Change in Eating Disorder Symptoms Following Pediatric Obesity Treatment. *Int. J. Eat. Disord.* **2019**, *52*, 299–303, doi:10.1002/eat.23015.
10. Tozzi, F.; Thornton, L.M.; Klump, K.L.; Fichter, M.M.; Halmi, K.A.; Kaplan, A.S.; Strober, M.; Woodside, D.B.; Crow, S.; Mitchell, J.; et al. Symptom Fluctuation in Eating Disorders: Correlates of Diagnostic Crossover. *Am. J. Psychiatry* **2005**, *162*, 732–740, doi:10.1176/appi.ajp.162.4.732.
11. Milos, G.; Spindler, A.; Schnyder, U.; Fairburn, C.G. Instability of Eating Disorder Diagnoses: Prospective Study. *Br. J. Psychiatry* **2005**, *187*, 573–578, doi:10.1192/bjp.187.6.573.
12. Castellini, G.; Lo Sauro, C.; Mannucci, E.; Ravaldi, C.; Rotella, C.M.; Faravelli, C.; Ricca, V. Diagnostic Crossover and Outcome Predictors in Eating Disorders According to DSM-IV and DSM-V Proposed Criteria: A 6-Year Follow-Up Study. *Psychosom. Med.* **2011**, *73*, 270–279, doi:10.1097/PSY.0b013e31820a1838.
13. Stice, E.; Marti, C.N.; Rohde, P. Prevalence, Incidence, Impairment, and Course of the Proposed DSM-5 Eating Disorder Diagnoses in an 8-Year Prospective Community Study of Young Women. *J. Abnorm. Psychol.* **2013**, *122*, 445–457, doi:10.1037/a0030679.
14. Jacobi, C.; Hayward, C.; de Zwaan, M.; Kraemer, H.C.; Agras, W.S. Coming to Terms with Risk Factors for Eating Disorders: Application of Risk Terminology and Suggestions for a General Taxonomy. *Psychol. Bull.* **2004**, *130*, 19–65, doi:10.1037/0033-2909.130.1.19.
15. Hilbert, A.; Pike, K.M.; Goldschmidt, A.B.; Wilfley, D.E.; Fairburn, C.G.; Dohm, F.-A.; Walsh, B.T.; Striegel Weissman, R. Risk Factors across the Eating Disorders. *Psychiatry Res.* **2014**, *220*, 500–506, doi:10.1016/j.psychres.2014.05.054.
16. Horwitz, T.; Lam, K.; Chen, Y.; Xia, Y.; Liu, C. A Decade in Psychiatric GWAS Research. *Mol. Psychiatry* **2019**, *24*, 378–389, doi:10.1038/s41380-018-0055-z.
17. The Brainstorm Consortium; Anttila, V.; Bulik-Sullivan, B.; Finucane, H.K.; Walters, R.K.; Bras, J.; Duncan, L.; Escott-Price, V.; Falcone, G.J.; Gormley, P.; et al. Analysis of Shared Heritability in Common Disorders of the Brain. *Science* **2018**, *360*, eaap8757, doi:10.1126/science.aap8757.
18. the Price Foundation Collaborative Group; Wang, K.; Zhang, H.; Bloss, C.S.; Duvvuri, V.; Kaye, W.; Schork, N.J.; Berrettini, W.; Hakonarson, H. A Genome-Wide Association Study on Common SNPs and Rare CNVs in Anorexia Nervosa. *Mol. Psychiatry* **2011**, *16*, 949–959, doi:10.1038/mp.2010.107.
19. Boraska, V.; Franklin, C.S.; Floyd, J. a. B.; Thornton, L.M.; Huckins, L.M.; Southam, L.; Rayner, N.W.; Tachmazidou, I.; Klump, K.L.; Treasure, J.; et al. A Genome-Wide Association Study of Anorexia Nervosa. *Mol. Psychiatry* **2014**, *19*, 1085–1094, doi:10.1038/mp.2013.187.
20. Duncan, L.; Yilmaz, Z.; Walters, R.; Goldstein, J.; Anttila, V.; Bulik-Sullivan, B.; Ripke, S.; Thornton, L.; Hinney, A.; Daly, M.; et al. Genome-Wide Association Study Reveals First Locus for Anorexia Nervosa and Metabolic Correlations. *Am. J. Psychiatry* **2017**, *174*, 850–858, doi:10.1176/appi.ajp.2017.16121402.
21. Li, D.; Chang, X.; Connolly, J.J.; Tian, L.; Liu, Y.; Bhoj, E.J.; Robinson, N.; Abrams, D.; Li, Y.R.; Bradfield, J.P.; et al. A Genome-Wide Association Study of Anorexia Nervosa Suggests a Risk Locus Implicated in Dysregulated Leptin Signaling. *Sci. Rep.* **2017**, *7*, 3847, doi:10.1038/s41598-017-01674-8.
22. Watson, H.J.; Yilmaz, Z.; Thornton, L.M.; Hübel, C.; Coleman, J.R.; Gaspar, H.A.; Bryois, J.; Hinney, A.; Leppä, V.M.; Mattheisen, M.; et al. Genome-Wide Association Study Identifies Eight Risk Loci and Implicates Metabo-Psychiatric Origins for Anorexia Nervosa. *Nat. Genet.* **2019**, *51*, 1207–1214, doi:10.1038/s41588-019-0439-2.

23. Martínez-Magaña, J.J.; Genis-Mendoza, A.D.; Villatoro Velázquez, J.A.; Bustos-Gamiño, M.; Juárez-Rojop, I.E.; Tovilla-Zarate, C.A.; Sarmiento, E.; Saucedo, E.; Rodríguez-Mayoral, O.; Fleiz-Bautista, C.; et al. Genome-Wide Association Study of Psychiatric and Substance Use Comorbidity in Mexican Individuals. *Sci. Rep.* **2021**, *11*, 6771, doi:10.1038/s41598-021-85881-4.
24. Ruiz-Ramos, D.; Martínez-Magaña, J.J.; García, A.R.; Juarez-Rojop, I.E.; Gonzalez-Castro, T.B.; Tovilla-Zarate, C.A.; Sarmiento, E.; López-Narvaez, M.L.; Nicolini, H.; Genis-Mendoza, A.D. Psychiatric Comorbidity in Mexican Adolescents with a Diagnosis of Eating Disorders Its Relationship with the Body Mass Index. *Int. J. Environ. Res. Public. Health* **2021**, *18*, 3900, doi:10.3390/ijerph18083900.
25. Martínez-Magaña, J.J.; Genis-Mendoza, A.D.; Villatoro Velázquez, J.A.; Camarena, B.; Martín del Campo Sanchez, R.; Fleiz Bautista, C.; Bustos Gamiño, M.; Reséndiz, E.; Aguilar, A.; Medina-Mora, M.E.; et al. The Identification of Admixture Patterns Could Refine Pharmacogenetic Counseling: Analysis of a Population-Based Sample in Mexico. *Front. Pharmacol.* **2020**, *11*, 324, doi:10.3389/fphar.2020.00324.
26. Nicolini, H.; Martínez-Magaña, J.J.; Genis-Mendoza, A.D.; Villatoro Velázquez, J.A.; Camarena, B.; Fleiz Bautista, C.; Bustos-Gamiño, M.; Aguilar García, A.; Lanzagorta, N.; Medina-Mora, M.E. Cannabis Use in People With Obsessive-Compulsive Symptomatology: Results From a Mexican Epidemiological Sample. *Front. Psychiatry* **2021**, *12*, doi:10.3389/fpsyt.2021.664228.
27. Garner, D.M.; Olmsted, M.P.; Bohr, Y.; Garfinkel, P.E. The Eating Attitudes Test: Psychometric Features and Clinical Correlates. *Psychol. Med.* **1982**, *12*, 871–878, doi:10.1017/s0033291700049163.
28. García-García, E.; Vázquez-Velázquez, V.; López-Alvarenga, J.C.; Arcila-Martínez, D. [Internal validity and diagnostic utility of the Eating Disorder Inventory in Mexican women]. *Salud Publica Mex.* **2003**, *45*, 206–210.
29. Spitzer, R.L.; Yanovski, S.; Wadden, T.; Wing, R.; Marcus, M.D.; Stunkard, A.; Devlin, M.; Mitchell, J.; Hasin, D.; Horne, R.L. Binge Eating Disorder: Its Further Validation in a Multisite Study. *Int. J. Eat. Disord.* **1993**, *13*, 137–153.
30. Spitzer, R.L.; Williams, J.B.; Gibbon, M.; First, M.B. The Structured Clinical Interview for DSM-III-R (SCID). I: History, Rationale, and Description. *Arch. Gen. Psychiatry* **1992**, *49*, 624–629, doi:10.1001/archpsyc.1992.01820080032005.
31. Endicott, J.; Spitzer, R.L. A Diagnostic Interview: The Schedule for Affective Disorders and Schizophrenia. *Arch. Gen. Psychiatry* **1978**, *35*, 837–844, doi:10.1001/archpsyc.1978.01770310043002.
32. Hartz, S.M.; Pato, C.N.; Medeiros, H.; Cavazos-Rehg, P.; Sobell, J.L.; Knowles, J.A.; Bierut, L.J.; Pato, M.T. Comorbidity of Severe Psychotic Disorders With Measures of Substance Use. *JAMA Psychiatry* **2014**, *71*, 248, doi:10.1001/jamapsychiatry.2013.3726.
33. Docherty, A.R.; Bigdeli, T.B.; Edwards, A.C.; Bacanu, S.; Lee, D.; Neale, M.C.; Wormley, B.K.; Walsh, D.; O'Neill, F.A.; Riley, B.P.; et al. Genome-Wide Gene Pathway Analysis of Psychotic Illness Symptom Dimensions Based on a New Schizophrenia-Specific Model of the OPCRIT. *Schizophr. Res.* **2015**, *164*, 181–186, doi:10.1016/j.schres.2015.02.013.
34. Pato, M.T.; Sobell, J.L.; Medeiros, H.; Abbott, C.; Sklar, B.M.; Buckley, P.F.; Bromet, E.J.; Escamilla, M.A.; Fanous, A.H.; Lehrer, D.S.; et al. The Genomic Psychiatry Cohort: Partners in Discovery. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **2013**, *162*, 306–312, doi:10.1002/ajmg.b.32160.
35. Purcell, S.; Neale, B.; Todd-Brown, K.; Thomas, L.; Ferreira, M.A.R.; Bender, D.; Maller, J.; Sklar, P.; de Bakker, P.I.W.; Daly, M.J.; et al. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *Am. J. Hum. Genet.* **2007**, *81*, 559–575.
36. Chang, C.C.; Chow, C.C.; Tellier, L.C.; Vattikuti, S.; Purcell, S.M.; Lee, J.J. Second-Generation PLINK: Rising to the Challenge of Larger and Richer Datasets. *GigaScience* **2015**, *4*, doi:10.1186/s13742-015-0047-8.
37. Conomos, M.P.; Miller, M.B.; Thornton, T.A. Robust Inference of Population Structure for Ancestry Prediction and Correction of Stratification in the Presence of Relatedness. *Genet. Epidemiol.* **2015**, *39*, 276–293, doi:10.1002/gepi.21896.
38. Harry, D. The Human Genome Diversity Project and Its Implications for Indigenous Peoples. *Genewatch Bull. Comm. Responsible Genet.* **1996**, *10*, 8–9.
39. McLaren, W.; Gil, L.; Hunt, S.E.; Riat, H.S.; Ritchie, G.R.S.; Thormann, A.; Flicek, P.; Cunningham, F. The Ensembl Variant Effect Predictor. *Genome Biol.* **2016**, *17*, doi:10.1186/s13059-016-0974-4.
40. Tian, D.; Wang, P.; Tang, B.; Teng, X.; Li, C.; Liu, X.; Zou, D.; Song, S.; Zhang, Z. GWAS Atlas: A Curated Resource of Genome-Wide Variant-Trait Associations in Plants and Animals. *Nucleic Acids Res.* **2020**, *48*, D927–

D932, doi:10.1093/nar/gkz828.
41. Domingo-Fernández, D.; Hoyt, C.T.; Bobis-Álvarez, C.; Marín-Llaó, J.; Hofmann-Apitius, M. ComPath: An Ecosystem for Exploring, Analyzing, and Curating Mappings across Pathway Databases. *Npj Syst. Biol. Appl.* **2018**, *4*, doi:10.1038/s41540-018-0078-8.
42. The Genotype-Tissue Expression (GTEx) Project. *Nat. Genet.* **2013**, *45*, 580–585, doi:10.1038/ng.2653.
43. GTEx Consortium Human Genomics. The Genotype-Tissue Expression (GTEx) Pilot Analysis: Multitissue Gene Regulation in Humans. *Science* **2015**, *348*, 648–660, doi:10.1126/science.1262110.
44. Rodríguez-López, M.L.; Martínez-Magaña, J.J.; Ruiz-Ramos, D.; García, A.R.; Gonzalez, L.; Tovilla-Zarate, C.A.; Sarmiento, E.; Juárez-Rojop, I.E.; Nicolini, H.; Gonzalez-Castro, T.B.; et al. Individuals Diagnosed with Binge-Eating Disorder Have DNA Hypomethylated Sites in Genes of the Metabolic System: A Pilot Study. *Nutrients* **2021**, *13*, 1413, doi:10.3390/nu13051413.
45. Manichaikul, A.; Mychaleckyj, J.C.; Rich, S.S.; Daly, K.; Sale, M.; Chen, W.-M. Robust Relationship Inference in Genome-Wide Association Studies. *Bioinforma. Oxf. Engl.* **2010**, *26*, 2867–2873, doi:10.1093/bioinformatics/btq559.
46. Dong, S.; Boyle, A.P. Predicting Functional Variants in Enhancer and Promoter Elements Using RegulomeDB. *Hum. Mutat.* **2019**, *40*, 1292–1298, doi:10.1002/humu.23791.