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Interaction of *FTO* rs9939609 and the native American-origin *ABCA1* p.Arg230Cys with circulating leptin levels in Mexican adolescents diagnosed with eating disorders: Preliminary results

Alma Delia Genis-Mendoza[a,b,g,*], José Jaime Martínez-Magaña[a,c,g], David Ruiz-Ramos[a,c,g], Vanessa Gonzalez-Covarrubias[d,g], Carlos Alfonso Tovilla-Zarate[e,g], Mari Lilia López Narvaez[f,g], Thelma Beatriz Gonzalez Castro[c,g], Isela Esther Juárez-Rojop[f,g], Humberto Nicolini[a,g,h,*]

[a] *Laboratorio de Genómica de Enfermedades Psiquiátricas y Neurodegenerativas, Instituto Nacional de Medicina Genómica, CDMX, México*
[b] *Hospital Psiquiátrico Infantil "Juan N. Navarro" Servicios de Administración Psiquiátrica, CDMX, México*
[c] *División Académica Multidisciplinaria de Jalpa de Méndez, Universidad Juárez Autónoma de Tabasco, Jalpa de Méndez, Tabasco, México*
[d] *Laboratorio de Farmacogenómica, Instituto Nacional de Medicina Genómica, CDMX, México*
[e] *División Académica Multidisciplinaria de Comalcalco, Universidad Juárez Autónoma de Tabasco, Comalcalco, Tabasco, México*
[f] *Hospital General de Yajalón Dr. Manuel Velasco Siles. Secretaria de Salud de Chiapas. Yajalón, Chiapas, Mexico*
[g] *División Académica de Ciencias de la Salud, Universidad Juárez Autónoma de Tabasco, Villahermosa, Tabasco, México*
[h] *Grupo de Estudios Médicos y Familiares Carracci, CDMX, México*

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ABSTRACT

Eating disorders (ED) are characterized by disruption of eating behaviour and alteration of food intake. Leptin, is one of the main hormones that modulate food intake and are altered in individuals diagnosed with ED. Genetic risk variants for obesity, like those reported in*FTO* and *ABCA1*, have also been associated to ED disorders. The present study aimed to analysed leptin circulating levels and the interaction between obesity-risk variants in *FTO* and *ABCA1*, in adolescents diagnosed with ED. A total of 99 individuals diagnosed with ED were genotype using Taqman probes for *FTO* (rs9939609) and *ABCA1* (p.Arg230Cys, rs9282541). Commercial enzyme-linked immunosorbent assays were utilized to determined circulating leptin. Differences in leptin concentration were analysed by t-Student or ANOVA test. Gene-gene interaction were analysed using general estimation equations. Circulating leptin levels differed between the three diagnostic groups, lead by individuals diagnosed with binge eating-disorder. In individuals with more than 3 of episodes of binge-eating per week having the highest leptin levels. Also, we found that carriers of both risk alleles had the highest leptin levels. Our observations found an interaction between *FTO* rs9969609 and the native American-origin *ABCA1* p.Arg230Cys to modulate circulating leptin levels in Mexican adolescents diagnosed with eating-disorders.

FTO: fat mass and obesity-associated gene.
ABCA1: ATP Binding Cassette Subfamily A Member 1 gene.
Log-leptin: log transformed circulating leptin levels.
p.Arg230Cys: aminoacid change of arginine by cysteine in position 230 *Abca1*.
Zscore of BMI: world health standardization of body mass index by age and sex.
rs9939609/rs9282541: national center for biotechnology dbSNP code for genetic polymorphism in *FTO* and *ABCA1*.
ED: eating-disorders.
BED: binge-eating disorders.
BN: bulimia nervosa.
AN: anorexia nervosa.
ELISA: enzyme-linked immunosorbent assay.
GWAS: genome-wide association studies.
QEWP: questionnaire on eating and weight patterns.
MINI: mini international neuropsychiatric interview.

1. Introduction

Eating disorders (ED), such as anorexia nervosa (AN), bulimia nervosa (BN) and binge eating (BED) are psychiatric affections

* Correspondence: Ph.D. Alma Delia Genis-Mendoza, Hospital Psiquiátrico Infantil "Juan N. Navarro", Servicios de Atención Psiquiátrica (SAP), Viaducto Tlalpan 74, Villa Lázaro Cárdenas, Zip code 14080, CDMX, México
E-mail addresses: adgenis@inmegen.gob.mx (A.D. Genis-Mendoza), hnicolini@inmegen.gob.mx (H. Nicolini).

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characterized by dysregulation of food intake and body weight (Herpertz et al., 2011; Sim et al., 2010). Underweight, overweight, or obesity, are frequently present as a common metabolic dysfunction in ED (da Luz et al., 2018; Star et al., 2015; Yu and Tan, 2016), with an apparent impact in adipose tissue (MacLean et al., 2015). Paradoxically, this adipose tissue, is a source of neuroendocrine hormones regulating appetite, such as leptin(Havel, 2000). Leptin, regulate long-term energy intake, by inhibiting food intake through signalling to the central nervous system (Campfield et al., 1995; Schwartz et al., 1996; Tang-Christensen et al., 1999; Tartaglia et al., 1995). Circulating leptin levels have been reported to be altered in patients with ED (Stroe-Kunold et al., 2016).

Recently, genome-wide association studies, reported loci associated to complex obesity and eating behaviours. Among these loci, some variants were found on *FTO* and *ABCA1*, suggesting the influence of genetic factors in these traits (Dina et al., 2007; Saldaña-Alvarez et al., 2016; Villalobos-Comparán et al., 2017; Villalobos-Comparán et al., 2008; Weissglas-Volkov et al., 2013). *FTO* and *ABCA1*, have shown to have an interaction in order to modulate obesity. The functional variant *ABCA1* p.Arg230Cys, was found to regulate HDL levels and obesity, has shown to be private to Native American populations (Acuña-Alonzo et al., 2010; Villalobos-Comparán et al., 2017). Variants on *FTO* and *ABCA1,* has been widely acknowledged to be associated to weight and have been reported to modulate eating behaviours (Micali et al., 2015; Müller et al., 2012). Heni et al., found that carriers of the obesity risk allele *FTO* rs9939609-A, had a lower inhibitory control of post-prandial feeding (Heni et al., 2013). These studies highlight the relevance of variants *FTO* rs9939609 and *ABCA1* p.Arg230Cys in weight modulation and eating disorders. However, the interaction of these genes to modulated leptin has not been explored. The aim of this study was to analyze the effect of these genetic variants and its potential association with circulating leptin levels in adolescents diagnosed with eating disorders.

2. Methods

2.1. Study population

Ninety-nine (n = 99) adolescents diagnosed with ED were recruited between May 2014 and August 2015 at the Hospital Psiquiátrico Infantil "Juan N. Navarro" in Mexico City. Diagnosis was assessed by an eating-disorder specialized psychiatrist, based on the DSM-5 criteria. We applied the Spanish version of the Questionnaire on eating and weight patterns (QEWP-5) (Yanovski et al., 2015). Psychiatric comorbidities were evaluated using the MINI-kid questionnaire (Sheehan et al., 1998; Sheehan et al., 2010). Inclusion criteria included individuals with at least three generations of Mexican ascendance, individuals with no psychoactive drugs (tobacco, alcohol or any drug use), psychiatric drugs (antidepressant, antipsychotic or mood stabilizer) prior to sample collection. Since, individuals were underage, they signed an informed assent and their parents an informed consent. The research ethics committee of the Instituto Nacional de Medicina Genómica and the Hospital Psiquiátrico “Infantil Juan N. Navarro” approved the protocol. Of the included individuals, 22 individuals (22.22%) complied with the criteria for anorexia nervosa (AN), 56 (56.56%) for bulimia nervosa (BN) and 21 (21.2%) for binge-eating disorders (BED) (Table 1). We observed a larger proportion of females compared to males (n = 69, 69.70% vs. n = 30, 30.3%. Also, we calculate the BMI by dividing weight (kg) by height (m) squared. We defined underweight, overweight, and obesity based on the 2007 WHO growth reference for school-age children and adolescents: underweight as zscore of BMI < -2 s.d, overweight as BMI zscore > 1 s.d and < = 2 s.d, and obese as BMI zscore > 2 s.d (de Onis et al., 2007; Hernández-Cordero et al., 2017). Most individuals, were underweight (n = 2, 2.02%), 13 individuals (13.13%) were overweight and 20 (20.20%) individuals had obesity. Other psychiatric disorders were diagnosed in 82 individuals (82.82%), being the most common, major depressive episode (n = 37, 37.37%), suicide risk (n = 22, 22.22%), attention-deficit/hyperactivity disorder (n = 36, 36.37%), and generalized anxiety disorder (n = 13, 13.13%).

Table 1
Sociodemographic and clinical characteristics of the sample.

	AN (n = 22)	BN (n = 56)	BED (n = 21)	Total (n = 99)
Gender				
Female	**16 (72.73)**	**44 (78.57)**	**9 (42.86)**	**69 (69.70)**
Male	**6 (27.27)**	**12 (21.43)**	**12 (57.14)**	**30 (30.30)**
Age	13.68 (2.17)	14.01 (1.95)	14.24 (1.55)	13.99 (1.91)
Years of school completed	9.00 (2.16)	8.54 (2.70)	8.33 (1.53)	8.60 (2.37)
Zscore of BMI	0.29 (0.80)	0.52 (0.77)	1.54 (0.89)	0.69 (0.92)
Log - Leptin	**1.65 (0.97)**	**2.01 (0.85)**	**2.40 (0.56)**	**2.01 (0.86)**
> 1 BE/week	**0 (0.00)**	**33 (58.93)**	**21 (100.0)**	**54 (54.54)**
> 1 Induced vomit/week	**5 (22.73)**	**39 (69.64)**	**0 (0.00)**	**44 (44.44)**
Restriction/week	**8 (36.36)**	**41 (73.21)**	**0 (0.00)**	**49 (49.49)**

Abbreviations: AN, anorexia nervosa; BN, bulimia nervosa; BED, binge eating disorder; Bold indicate significant statistical p-value <0.05

2.2. Circulating leptin measurement

Leptin concentration in plasma was assessed from a blood sample collected in the morning after 7 hours of fasting using a commercial enzyme-linked immunosorbent assay (ELISA) and a (Leptin Human ProcartaPlex, eBioscience, Austria), according to the manufacturers protocol in a Epoch2 spectrophotometer (BioTek, USA). Leptin concentration were reported as the average of duplicate measurements from the interpolation to the standard curve.

2.3. Genotyping

DNA was isolated from peripheral leukocytes, using a commercial salting-out modified method (Qiagen, USA). We performed direct genotyping of variants rs9939609 (*FTO, NM_001363894.1:c.*) and rs9282541 (*ABCA1, NP_005493.2:p.Arg230Cys*) using TaqMan assays according to manufacturer's protocol (Applied Biosystems, USA). We used the GWAS catalog to define the risk-allele for both polymorphisms (Buniello et al., 2019). For both polymorphisms, the A allele was the risk variant. In the case of *FTO* rs9939609, located in an intronic position, the rs9939609-A risk-allele has been associated to BMI and obesity in different populations (Dina et al., 2007; Villalobos-Comparán et al., 2008; Wang et al., 2013). Meanwhile, the rs9282541-A risk-allele has been associated to a reduction in HDL-cholesterol only in Hispanic populations (Weissglas-Volkov et al., 2013). *ABCA1,* rs9282541-A is an aminoacidic change of arginine (R) for cysteine (C) in the position 230 of *ABCA1* protein (*ABCA1, NP_005493.2:p.Arg230Cys*). To date, the variant rs9282541-A has been found only in Native American groups or Mexican-Mestizo population (Villareal-Molina et al., 2007; Wang et al., 2000).

2.4. Statistical analyses

We tested normality distribution for leptin concentrations using the Shapiro-Wilkins test. The log-transformed of circulating leptin levels were used for statistical analyses (showed a normal distribution). In addition, we calculate the index weight/log-leptin. Hardy-Weinberg equilibrium and genotype differences between AN, BN, and BE study groups were analysed using a Fisher test. Next, individuals were grouped if bearing the risk-allele i.e. individuals with an A allele (homozygous or heterozygous) were classified as *FTO* or *ABCA1*

Table 2
Allelic and genotype frequencies of genetic polymorphisms.

	AN (n = 22)	BN (n = 56)	BED (n = 21)	MAF	gnomAD	gnomAD Latino
FTO (rs9939609)	0.25 (A/A = 2, A/T = 7, T/T = 13)	0.19 (A/A = 2, A/T = 17, T/T = 37)	0.24 (A/A = 1, A/T = 8, T/T = 12)	0.21 (A/A = 5, A/T = 32, T/T = 62)	0.4162	0.2541
ABCA1 (p.Arg230Cys)	0.18 (A/G = 4, G/G = 18)	0.10 (A/G = 11, G/G = 45)	0.17 (A/G = 7, G/G = 14)	0.11 (A/A = 0, A/G = 22, G/G = 77)	0.0116	0.0904
Carrier FTO/ABCA1	0.14 (n = 3)	0.07 (n = 4)	0.19 (n = 4)	0.11 (n = 11)		
Carrier FTO/ Non Carrier ABCA1	0.27 (n = 6)	0.33 (n = 15)	0.23 (n = 5)	0.26 (n = 26)		
Non Carrier FTO/ Carrier ABCA1	0.05 (n = 1)	0.13 (n = 7)	0.14 (n = 3)	0.11 (n = 11)		
Non Carrier FTO/ABCA1	0.54 (n = 12)	0.54 (n = 30)	0.43 (n = 9)	0.51 (n = 51)		

Abbreviations: AN, anorexia nervosa; BN, bulimia nervosa; BED, binge eating disorder

carriers. Differences between groups were assessed using a t Student or an ANOVA test. We defined a threshold of p-vale < 0-05 as statistically significant. Also, we investigated the interaction between both polymorphism and log-leptin was tested with general estimation equations. Also, correlation between quantitative variables were analysed by Pearson correlation tests. When considering genetic associations, a p-value lower than 0.025 (0.05 / 2 genotyped SNPs) as statistical significant was defined. All the statistical analyses were performed using R (R Team, 2013).

3. Results

3.1. Circulating leptin levels

The mean level of log-leptin was 2.01 (range = 1.57 to 2.59), these did not differ between males and females (t = 1.77, p-value: 0.0821). Leptin concentrations were not correlated with age (Pearson r-square = - 0.03, p-value = 0.6112), but with BMI (Pearson r-square = 0.22, p-value = 0.0414). After stratification by ED diagnosis, log-leptin levels differed between the different diagnoses of ED (F = 4.361, p-value = 0.0082) (Fig. 1). Individuals diagnosed with AN showed the lowest leptin levels of log-leptin (mean = 1.65, s.d = 0.97), followed by individuals diagnosed with BN (mean = 2.04, s.d = 0.85) and BED (mean = 2.28, s.d = 0.56). Analysing, the log-leptin levels, by the different symptoms of ED (restriction, binge-eating and vomit). Interesting, log-leptin concentrations differed by binge-eating number of episodes per week (t = - 3.14, p-value = 0.0025), individuals with at least one episode showed the higher levels of leptin (mean = 2.23, s.d = 0.71), compared to those without any episode (mean = 1.68, s.d = 0.97). Individuals with more than 3 episodes of binge-eating by week had the higher levels of log-leptin (mean = 2.53, s.d = 0.71, p-value = 0.0025). For patients with more than 3 binge episodes (n = 20, 20.20%), 17 individuals (85.00%) were females and 3 males (15.00%). The age did not differed between the individual, with more than 3 binge-episodes (mean = 14.15, s.d. = 1.69), neither the zscore of BMI (mean = 0.93, s.d. = 0.97). Regarding the genotype, only 2 (2.02%) individuals carriers the rs9282541-A, and 6 (6.06%) the rs9939609-A.

After stratification by psychiatric comorbidities, we found that, only individuals with anxiety disorder showed different levels of log-leptin compared to those that did not have the comorbidity. Individuals with generalized anxiety disorder had a higher level of log-leptin (mean = 2.59, s.d = 0.56 versus than does that did not have generalized anxiety disorder (mean = 1.93, s.d = 0.86).

3.2. FTO and ABCA1 polymorphisms

The allele frequency of the A allele of *FTO* obesity risk polymorphism rsrs9939609 and *ABCA1* rs9282541 were 0.21 and 0.11. Variant *ABCA1* rs9282541-A did not showed any homozygous for the A allele. Allele frequencies were similar between study groups and none showed an association with psychiatric comorbidities. Interesting in this sample we did not find an association of rs9969609-A (t = - 0.56, p-value = 0.8585) or rs9282541-A (t = 0.3069, p-value = 0.5514), with the zscore of BMI.

We observed an association between *ABCA1* rs9282541-A and the ratio of weight/log-leptin (t = 2.60, p-value = 0.0134). Carriers of the A allele showed a higher weight/log-leptin index (mean = 0.0435, s.d = 0.0141) compared to non-carriers (mean = 0.0340, s.d = 0.0169).

3.3. Impact of FTO and ABCA1 genotypes on leptin circulating levels

We observed normalized log-leptin levels differences in carriers of the risk alleles *ABCA1* rs9282541-A (t = 2.76, p-value = 0.0091), but no differences were observed for carriers of the *FTO* rs9969609-A

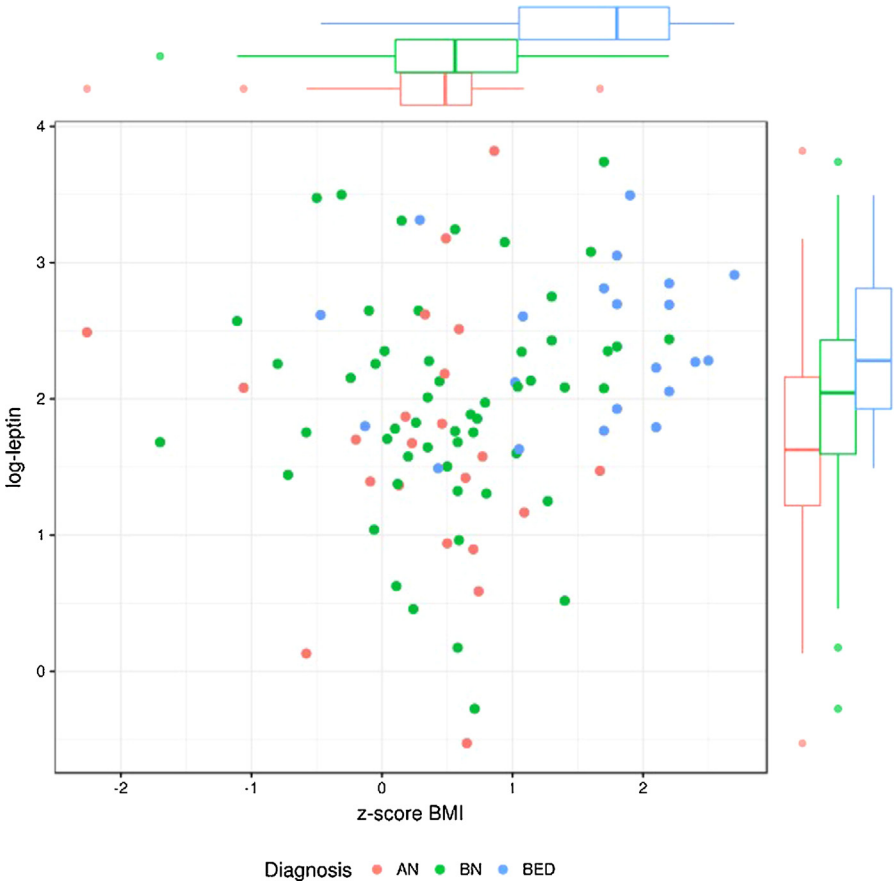

Fig. 1. Correlation between zscore of BMI and circulating leptin. In the superior boxplot the distribution of zscore of BMI is presented by diagnosis subgroups of ED is presented, in blue is binge-eating disorder (BED), green is bulimia nervosa (BN) and red in anorexia nervosa (AN). In the lateral boxplot the distribution of log transformed circulating leptin (log-leptin) by diagnosis subgroups of ED is presented. The correlation between zscore of BMI and log-leptin reached statistical significance (Pearson r-square = 0.22, p-value = 0.0414). After stratification by ED diagnosis, log-leptin levels differed between the different diagnoses of ED (F = 4.361, p-value = 0.0082), and also, the zscore of BMI differed (F = 10.34, p-value = 0.0001).(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

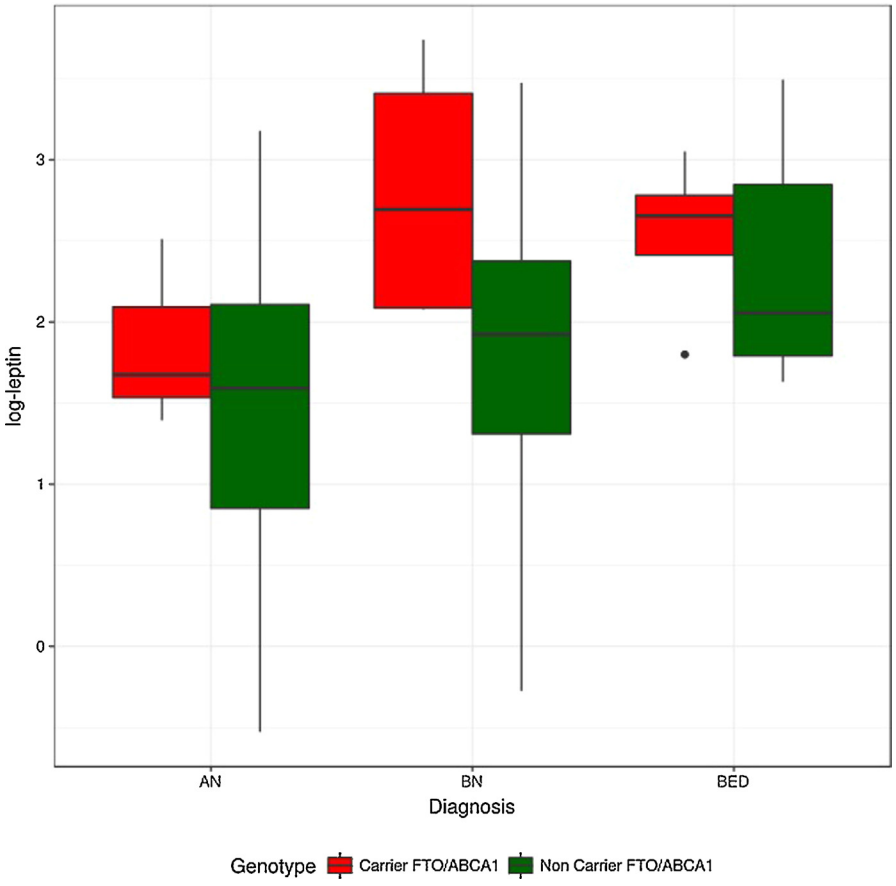

Fig. 2. Interaction of obesity-risk *FTO* and p.Arg230Cys *ABCA1* variants and circulating leptin. The boxplot represented the log transformed circulating leptin (log-leptin) is stratified by the diagnosis subgroups of ED, and by the status of the obesity-risk variants. Carrier *FTO/ABCA*1 represented individuals that carriers both obesity-risk alleles (rs9939609-A and rs9282541-A) in homozygous or heterozygous state, meanwhile, Non Carrier *FTO/ABCA1* represented individuals not carrier of any of the obesity-risk variants.

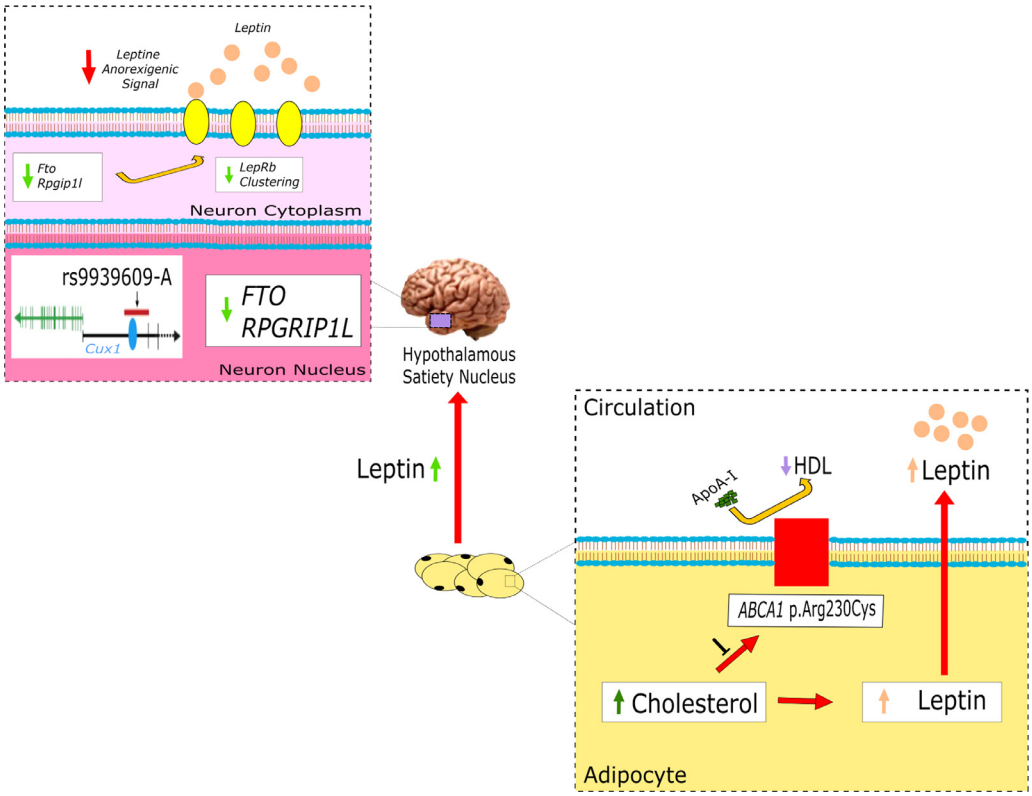

Fig. 3. Possible link between the p.Arg230Cys *ABCA1* and rs9939609-A *FTO* genetic variants (brain - adipose). *ABCA1* p.Arg230Cys could reduce the cholesterol efflux to the nascent HDL particles, promoting an accumulation in adipocyte under a high-fat diet. The increase of cholesterol, promotes an over expression of leptin. The over-expression of leptin could increase the circulating leptin levels. Meanwhile, in the brain *FTO* rs9939609-A, could disturb the binding site of *CUX1*, reducing the expression of *FTO* and *RPGIP1L*. This reduction, also reduces the clustering of the leptin receptors at the hypothalamus satiety center, promoting a leptin resistant phenotype.

obesity-risk allele (t = 1.53, p-value = 0.2327). Considering both polymorphisms, *FTO* and *ABCA1* carriers of the A allele showed the highest levels of log-leptin (mean = 2.45, s.d = 0.72) compared to non-carriers (mean = 1.81, s.d = 0.91) (p-value of interaction = 0.0466). After stratification by diagnosis, we found that individuals with BN and carriers of the A allele in both *FTO* and *ABCA1* variants consistently showed the highest log-leptin (p-value = 0.0490, Fig. 2). Patients with AN or BED showed a trend towards these differences but did not reach statistical significance. Interestingly, the zscore of BMI was significantly different between carriers of both alleles compared to non-carriers in the individuals with BN (t = 3.33, p-value = 0.0159).

4. Discussion

Individuals diagnosed with eating-disorders show significant changes in eating behaviour, circulating neuroendocrine hormones, body weight, etc., which leads to important metabolic alterations. In this study we analysed if relevant polymorphisms n *FTO* and *ABCA1,* involved in the regulation of adiposity, could be associated to leptin levels in plasma, since differences in this hormone would explain in part differences in BMI frequently observed in these patients. We identified that leptin levels differed among individuals with distinctive ED diagnosis. For example, AN diagnosed individuals had the lowest leptin levels while BED diagnosed individuals showed the highest leptin levels. Our results are in agreement with previous studies as the increase in circulating leptin levels in individuals with binge-eating behaviour and the lower levels in individuals with anorexia, have been reported in adolescents and adults (Adami et al., 2002; Miller et al., 2014; Stroe-Kunold et al., 2016). Higher circulating leptin levels could be consistent with reduction in adiposity in individuals with ED, as previous reports correlate leptin with obesity and long-term positive energy, suggesting that steadily high leptin reflects an increase in adipocyte mass (Frederich et al., 1995). Our analyses, identified a correlation between the zscore of BMI, a proxy indicator of adiposity, and leptin levels. This could be indicative that individuals with a lower BMI zscore have the higher circulating leptin levels meaning that signalling from the adipose tissue in order to control energy intake is possible normal in these individuals. Patients with BN and BED showed increased leptin levels and increase in food intake could be pointing to a deregulation in the brain of the signal emitted by leptin to reduce food intake, pointing to a possible leptin resistance mechanism in patients with BED or BN. This could pinpoint the individuals with more frequent binge-episodes have higher levels of circulating leptin. Nevertheless, this hypothesis for leptin resistance development ought to be tested in-vitro and confirmed by other studies, the mechanism by how this leptin resistance is developed remain unknown, but some hypothesis could be stated. Leptin main function is to modulate energy homeostasis, and has been implicated in brain-reward mechanisms (Figlewicz and Benoit, 2009; Shen et al., 2016), likely by modulating dopaminergic activity through a bimodal regulation i.e. low leptin levels sustain dopamine-dependent brain signals, while increased levels could disrupt them (Hickey et al., 1996). The increase of leptin levels in individuals with BED or BN, could be creating a positive loop between brain and adipocytes, potentially to sustain this reward dopamine-dependent brain signals and promoting an increased food intake, observed in individuals with more episodes of binge-eating. Additionally, brain alterations in areas sensing leptin could be part of a synergic reward/food intake loop. In this regard, genetic polymorphisms could be influencing the reward dopamine-dependent brain signals, previously associated to complex obesity, like *FTO* or *ABCA1* (Dina et al., 2007; Hung et al., 2014; Scuteri et al., 2007). For example, de Groot et al identified an association between *FTO* rs9939609-A allele carriers and a lower volume in the nucleum accumbens, one of the brain areas involved in modulating reward dopamine-dependent signals (de Groot et al., 2015). The latter reinforces the idea that obesity associated polymorphisms could contribute to alterations in brain structures. A *ABCA1* loss-of-function mice model seemed to exert neuron structure alterations and differences in brain cholesterol homeostasis (Karasinska et al., 2009), suggesting that loss of function of *ABCA1* could reduce HDL brain levels, and thus, cholesterol homeostasis and brain function. In humans, the interaction

between *ABCA1* and *FTO* genetic polymorphisms has shown to reduce circulating levels of HDL (Villalobos-Comparán et al., 2017). Here, we found that these two same polymorphisms are also associated with circulating leptin and BMI in adolescents with ED diagnosis. These observations could highlight the presence a possible mechanism mediated by obesity-risk genetic variants and the regulation of leptin potentially influencing appetite signals. In this study, carriers of *FTO* and *ABCA1* obesity risk variants showed the highest levels of leptin in all study groups including individuals with AN, were the leptin resistance is potentiated by the interaction of the both obesity-risk alleles.

The functional mechanism by which *FTO* and *ABCA1* genetic polymorphisms might be promoting leptin resistance is still unknown. We could hypothesize that there is an interaction of these genetic variants and the appetite neuroendocrine signals regulated by adipose tissue, where *ABCA1* p.Arg230Cys increases leptin and *FTO* rs9939609 could be promoting a leptin resistance in the brain (Fig. 3). Next, we will highlight some works supporting our hypothesis in this genetic interaction. *ABCA1* transports cholesterol to Apolipoprotein A-1 in adipocytes, the functional impact of variant *ABCA1* p.Arg230Cys, decreases *ABCA1* activity thus, lowering cholesterol efflux, consequently lowering the formation of nascent HDL and accumulating intracellular cholesterol (Acuña-Alonzo et al., 2010; Ishigami et al., 2019). *ABCA1* loss-of-function mice under a high-fat diet, showed an increase in intracellular cholesterol and triglycerides storage in adipocytes accompanied by an increase in body weight (de Haan et al., 2014). Furthermore, in this model, *lep* (leptin) and *glut-4* were dysregulated, causing a higher expression of leptin, and a reduction of *glut-4* (glucose transporter - 4), both key regulators of food intake and glucose tolerance. Increased circulating levels of leptin could be expected if *lep* expression is increased. Therefore, it is possible to expect that carriers of *ABCA1* p.Arg230Cys could yield a higher amount of leptin, especially in individuals with BED and BN, where we found the highest prevalence of obesity. In addition, the dysregulation of the glucose transporters like GLUT-4, could be pointing to the possible relationship between *ABCA1* p.Arg230Cys in type II diabetes which in turn can be modulated by HDL in Mexican patients (Ochoa-Guzman et al., 2020). We suggest that *ABCA1* p.Arg230Cys and *FTO* rs9939609 may be acting in synergy, since *ABCA1* p.Arg230Cys impact may increase leptin expression in adipocytes and likely its circulating levels, meanwhile *FTO* rs9939609, reduces the sensibility of appetite sensing brain areas to circulating leptin. *FTO* rs9939609 variant is intronic and reports indicate that it is associated with a reduced brain sensitivity to this leptin at the hypothalamus, consequently increasing the resistance to leptin. The obesity-risk variant *FTO* rs9939609 is on the first intron, disturbing the binding site of *CUX1,* a transcription factor that modulates *FTO* and the adjacent gene, *RPGIP1L*, expression (Stratigopoulos et al., 2011). A less tight union between *CUX1* and *FTO* reduces the expression of both genes in the hypothalamus, which promotes a smaller cluster of leptin receptors giving rise to the obese, hyperphagic phenotype in mice (Stratigopoulos et al., 2016). Reinforcing the fact of a possible interaction between these genetic variants.

Our hypotheses are based on a small study and it lacks of a control, non-ED group to validate in-depth this association. Moreover, life-style information was also lacking preventing the consideration of diet and exercise influencing leptin levels. Nevertheless, we explored an interesting relationship between specific *FTO* and *ABCA1* genetic variations and leptin levels which has not been previously reported. Our observations warrant replication in larger cohorts, and could be considered as preliminary. These results offer information for future studies to dissect the pathways controlling appetite and reward signalling in brain and its association with genetic variation. Investigation of genetic variants private to specific populations offer new hypothesis on the evolution of a common metabolic pathways to different continental populations as is the case for p.Arg230Cys in *ABCA1*, present only in people of the Americas.

In conclusion, we found an interaction between *ABCA1* p.Arg230Cys and *FTO* rs9939609 with circulating leptin levels, in patients diagnosed with eating disorders suggesting a potential role of specific genetic variation in the regulation of appetite.

CRediT authorship contribution statement

Alma Delia Genis-Mendoza: Conceptualization, Formal analysis, Funding acquisition, Project administration, Software, Writing - original draft. **José Jaime Martínez-Magaña:** Conceptualization, Formal analysis, Funding acquisition, Project administration, Software, Writing - original draft. **David Ruiz-Ramos:** Data curation, Investigation, Methodology, Writing - review & editing. **Vanessa Gonzalez-Covarrubias:** Data curation, Investigation, Methodology, Writing - review & editing. **Carlos Alfonso Tovilla-Zarate:** Data curation, Investigation, Methodology, Writing - review & editing. **Mari Lilia López Narvaez:** Data curation, Investigation, Methodology, Writing - review & editing. **Thelma Beatriz Gonzalez Castro:** Data curation, Investigation, Methodology, Writing - review & editing. **Isela Esther Juárez-Rojop:** Data curation, Investigation, Methodology, Writing - review & editing. **Humberto Nicolini:** Conceptualization, Formal analysis, Funding acquisition, Project administration, Software, Writing - original draft.

Declaration of Competing Interests

The authors declare no conflict of interest.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Instituto Nacional de Medicina Genómica research committee (06/2018/I) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed assent was obtained from all the individuals participants included in the study. Also, informed consent was obtained from all parents of the individual participants included in the study.

Contribution Statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Alma Delia Genis-Mendoza and José Jaime Martínez-Magaña. The first draft of the manuscript was written by Alma Delia Genis-Mendoza and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in

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