Association of the Arg51Gln Polymorphism of the Ghrelin Gene and Serum Ghrelin levels with overweight and obesity in young individuals

Asociación del polimorfismo Arg51Gln del gen de grelina y de los niveles séricos de grelina con sobrepeso y obesidad en población joven

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The research contributes to understanding the genetic (Arg51Gln polymorphism) and biochemical (serum ghrelin levels) factors influencing obesity and overweight, particularly in a young population from Western Mexico. The research offers insights into the monomorphic nature of the Arg51Gln polymorphism in the Western Mexican population, which is crucial for understanding genetic influences on obesity in specific demographics. Role of Ghrelin: Understanding ghrelin's role in regulating appetite and energy balance and its association with body weight and fat distribution. Genetic Variations: Comprehending how specific genetic polymorphisms (e.g., Arg51Gln) affect ghrelin secretion and activity, and how these variations influence obesity. Population-Specific Genetic Expressions: Recognizing that genetic factors influencing obesity may vary significantly across different populations, which necessitates studying diverse demographic groups. Hormonal and Metabolic Interactions: Investigating how hormonal levels (like ghrelin) interact with metabolic processes and contribute to conditions like overweight and obesity.

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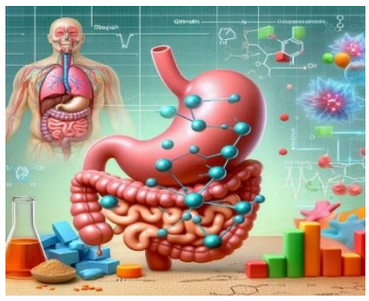
Abstract

Obesity and overweight are growing public health concerns, especially among young people. Ghrelin, an appetite-regulating hormone, and the Arg51Gln polymorphism in the ghrelin gene have been associated with obesity. Methodology: Serum ghrelin levels and the Arg51Gln polymorphism were studied in 289 university students from western Mexico. Anthropometric measurements and blood samples were taken to analyze ghrelin levels and genotype the polymorphism. Results: The polymorphic allele (T) was not found in the participants; all were homozygous for the wild-type allele (C/C). Ghrelin levels were higher in the obesity group and lower in the overweight group. A significant association was found between ghrelin levels and overweight, but not with obesity. Conclusions: Serum ghrelin levels are associated with overweight in young individuals, but the Arg51Gln polymorphism is not present in this population. These findings may inform prevention and treatment strategies for obesity**.**

Association of the Arg51Gln Polymorphism of the Ghrelin Gene and Serum Ghrelin Levels with Overweight and Obesity in young individuals		
Objectives	**Methodology**	**Contribution**
		
Describe the association of ghrelin and the Arg51Gln polymorphism with overweight and obesity in young populations	*Selection of young subjects with overweight and obesity *Determination of Ghrelin by sandwich ELISA *Characterization of the polymorphism through real-time PCR	Joint analysis of obesity with ghrelin Evidence of the possible existence of the monomorphic region for this coding zone in the Mexican population from the western region

These images were created with AI Dall-E

Obesity, Ghrelin, Polymorphism

Resumen

La obesidad y el sobrepeso son crecientes preocupaciones de salud pública, especialmente entre los jóvenes. La grelina, una hormona reguladora del apetito, y el polimorfismo Arg51Gln se han asociado con la obesidad. Metodología: Se estudiaron los niveles séricos de ghrelina y el polimorfismo Arg51Gln en 289 jóvenes del occidente de México. Se tomaron medidas antropométricas y muestras de sangre para analizar los niveles de grelina y realizar la genotipificación del polimorfismo. Resultados: No se encontró el alelo polimórfico, todos fueron homocigotos para el alelo de tipo salvaje. Los niveles de ghrelina fueron más altos en el grupo con obesidad y más bajos en el grupo con sobrepeso. Se encontró una asociación significativa entre los niveles de ghrelina y el sobrepeso, pero no con la obesidad. Conclusiones: Los niveles séricos de ghrelina están asociados con el sobrepeso en jóvenes. Estos hallazgos pueden informar estrategias de prevención y tratamiento de la obesidad.

Asociación del polimorfismo Arg51Gln del gen de grelina y de los niveles séricos de grelina con sobrepeso y obesidad en población joven		
Objetivos	**Metodología**	**Contribución**
		
Describir la asociación de grelina y el polimorfismo Arg51Gln con sobrepeso y obesidad en población joven	*Selección de sujetos jóvenes son sobrepeso y obesidad *Determinación de Grelina por ELISA tipo sándwich *Caracterización del polimorfismo a través de PCR en tiempo real	Análisis de forma conjunta de obesidad con grelina Evidencia de la posible existencia de la región monomórfica para esta zona codificante en población mexicana del occidente

Estas imágenes fueron creadas con AI Dall-E

Obesidad, Grelina, Polimorfismo

Introduction

Obesity and overweight are growing public health concerns worldwide, particularly among young adults, including university students. Understanding the genetic and biochemical factors that contribute to these conditions is crucial for developing effective prevention and treatment strategies. Ghrelin, a peptide hormone primarily produced in the stomach, plays a significant role in regulating appetite and energy balance. Variations in the ghrelin gene, particularly the Arg51Gln polymorphism, have been implicated in influencing ghrelin levels and potentially contributing to obesity.

The Arg51Gln polymorphism results from a single nucleotide change that replaces arginine (Arg) with glutamine (Gln) at position 51 in the ghrelin peptide. This genetic variation has been associated with altered ghrelin secretion and activity, which may influence body weight and fat distribution. Additionally, serum ghrelin levels, which regulate hunger and energy intake, may differ among individuals with varying body mass indices (BMI).

This study aims to describe the association of serum ghrelin levels and the Arg51Gln polymorphism of the ghrelin gene with overweight and obesity in young individuals from Western Mexico. By investigating these associations, we seek to contribute to the understanding of the genetic and biochemical factors underlying obesity in this population.

We hypothesize that there is an association between serum ghrelin levels and/or the Arg51Gln polymorphism of the ghrelin gene with overweight and obesity in university students from Guadalajara. This hypothesis is based on previous studies that have shown a link between ghrelin gene polymorphisms, ghrelin levels, and body weight regulation. Our research will provide further insights into the potential genetic and hormonal mechanisms influencing obesity in young adults, which may inform targeted interventions and therapeutic approaches.

In this chapter, we present the results of our research and explore the topics of obesity and overweight, satiety and intake control, ghrelin and related diseases, genetic variants of the ghrelin gene, the Arg51Gln polymorphism, and metabolic diseases in young populations.

Development

Overweight and Obesity

Recent statistics indicate that overweight and obesity continue to rise globally, with more than 2 billion people worldwide having excess weight, accounting for approximately 30% of the global population (Caballero, 2019; WHO, 2024). In Latin America, according to the latest joint report presented in the Panorama of Food and Nutrition Security in Latin America and the Caribbean, about 16% of the population is obese, and slightly over 43% are overweight, resulting in a combined prevalence of nearly 60%. The impact is more significant among women and shows an upward trend in adolescents and young adults (OPS, 2024). Meanwhile, in Mexico, the 2022 National Health and Nutrition Survey reported a combined prevalence of overweight and obesity of 75.2%. Notably, the prevalence of obesity increased by 21.4% from 2006 to 2022 (INSP, 2023).

Obesity is a complex and multifactorial condition affecting millions of people worldwide and significantly contributing to the burden of morbidity. It is associated with various pathologies, including cardiovascular diseases, type 2 diabetes, hypertension, and certain types of cancer (Erion et al., 2017). Its etiology involves genetic and environmental factors, as well as lifestyle factors such as dietary habits, physical inactivity, and the nature of food consumed (INSP, 2024). Excess weight is attributed to an imbalance between caloric intake and energy expenditure, leading to chronic excessive accumulation of adipose tissue (Erion et al., 2017).Energy metabolism and appetite regulation are influenced by a complex network of hormonal and neuroendocrine signals (Lustig et al., 2022). Multiple hypothalamic regions send and receive signals from the insula, orbitofrontal cortex, nucleus accumbens, and the dopaminergic reward system, as well as chemical signals, including peptides and gastrointestinal hormones, to regulate eating behavior (Van Loenen et al., 2020). Among these signals, ghrelin, known as the "hunger hormone," plays a crucial role due to its orexigenic effect.

Ghrelin

Ghrelin is a peptide hormone composed of 28 amino acids requiring an essential enzymatic modification (O-acyltransferase) to enable its bioactivity and ability to activate one of the two ghrelin receptors. Two different ghrelin receptors have been identified: GHS-R1a and GHS-R1b (Van Loenen et al., 2020). This hormone is primarily produced in the stomach but can also be found in small concentrations in the hypothalamus. It promotes food intake and regulates energy homeostasis by acting on the hypothalamus to increase appetite and stimulate the release of growth hormone (Ibrahim et al., 2023).

The activation of GHS-R1a by ghrelin induces multiple cells signaling pathway cascades, which can, in turn, regulate a wide range of metabolic processes such as gluconeogenesis and fat deposition (Van Loenen et al., 2020). Interestingly, ghrelin levels are shown to be reduced in the context of obesity and a high-fat, high-sugar diet. Ghrelin acts on all body systems, with well-known effects involving the regulation of the gut-brain axis, including appetite, food intake, energy, and glucose metabolism, which are key factors leading to obesity (Ibrahim et al., 2023).

Some studies indicate that ghrelin is a potent stimulator of growth hormone (GH) secretion, which leads to insulin suppression by glucose action. Ghrelin synthesized in the islets of Langerhans restricts insulin release (Dezaki, 2015). It has also been linked to Metabolic Syndrome (MS). The OPERA study showed a negative correlation between ghrelin levels and the number of MS components. MS itself decreased ghrelin levels as the number of MS components increased. Recently, it has been found that as the number of MS parameters increases, there is a reduction in circulating acylated ghrelin, while desacylated ghrelin increases. However, it remains unclear whether this association is causal and its behavior in apparently healthy individuals (Mora et al., 2015).

Ghrelin gene

The coding of the ghrelin gene and its genomic structure has allowed for detailed scrutiny of the gene. This has increased interest in the potential role of the ghrelin gene in regulating risk in various pathologies, including obesity and lipid metabolism disorders, as well as inflammatory and metabolic diseases such as metabolic syndrome, insulin resistance, and diabetes mellitus.

Ghrelin is encoded by the GHRL gene, and genetic variations in this gene can influence serum ghrelin levels and, consequently, body weight regulation (Becer & Ergoren, 2021). The best-known SNPs are Arg51Gln, located in the region that regulates the generation of the active mature hormone, and Leu72Met and Gln90Leu, located elsewhere in the gene (Mora et al., 2015).

Arg51Gln polymorphism (rs34911341)

Arg51Gln is located in exon 2 of the ghrelin gene. This polymorphism involves an amino acid change from arginine (Arg) to glutamine (Gln) at position 51, which can alter ghrelin's functionality and its interaction with the receptor (Pöykko, 2003). The Arg51Gln polymorphism (rs34911341) has been studied in various populations due to its potential impact on susceptibility to obesity and overweight (Becer & Ergoren, 2021).

Previous studies have explored the relationship between the Arg51Gln polymorphism and serum ghrelin levels, as well as its association with anthropometric parameters in various cohorts. However, the results have been inconsistent, and the influence of this polymorphism in specific populations, such as young individuals, is not yet fully understood. Given the importance of the young adult population in preventing long-term obesity and its comorbidities, it is crucial to better understand the genetic and hormonal factors contributing to overweight and obesity at this life stage.

This study aims to investigate the association of the Arg51Gln polymorphism of the ghrelin gene and serum ghrelin levels with overweight and obesity in a young population. Identifying these associations could provide a deeper understanding of the mechanisms underlying body weight regulation and offer new perspectives for preventive and therapeutic strategies in the fight against obesity.

Methodology

Before the beginning of the study, we shared the necessary information with students who met the inclusion criteria. Inclusion criteria were: 18 – 25 years, fasting 8 – 10 hours, BMI ≥ 19 Kg/m^2, not related with other participant of the study, sign inform consent and participated volunteer. Those who decided to participate were received in the Biochemistry Laboratory between 8:00 and 10:00 in the morning. Upon arrival, those meeting the inclusion criteria filled out a clinical history form. We took anthropometric measurements (weight, height) for BMI calculations. After that, a blood sample was taken in two different tubes for analysis. One tube was used to quantify serum ghrelin, and the other was used for DNA extraction to characterize the Arg51Gln polymorphism.

Body max index calculations.

For weight, we used a TANITA scale 300A with participants barefoot, standing, and recorded the weight in kilograms (kg). Height was measured with a stadiometer, with participants standing with heels together, arms at their sides, and their backs against a flat surface, recorded in meters. This data was used to calculate BMI, which is calculated by dividing the weight in kilograms by the height squared in meters. We used this calculation to divide the population into three groups: those with normal weight (19.0 kg/m^2 – 24.5 kg/m^2), overweight (25.0 kg/m^2 – 29.9 kg/m^2), and obesity (> 30.0 kg/m^2) according to WHO standards

Ghrelin serum levels assay

One of the blood samples was centrifuged to obtain serum, which was separated into aliquots of 500 µL in Eppendorf microtubes and frozen at -20°C for analysis once all volunteers were recruited. The stability of the samples is 6 months at frozen temperatures, avoiding freeze-thaw cycles. Once we completed the sample size, analysis was performed by immunoassay using the Magpix Luminex with the Bio-Plex 200 System Assay Human Diabetes kit, according to the manufacturer's specifications.

DNA Extraction

DNA from leukocytes was extracted using the modified Miller salt precipitation method. The obtained DNA was reconstituted with 0.3 mL of Tris-EDTA (T.E.) buffer and stored at -76°C (Miller, 1998)

DNA Quantification

The obtained DNA was analyzed by spectrophotometry to quantify concentration and purity. After that, it was homogenized with sterile water and separated into aliquots with a final concentration of 100 ng/µL to be used in the characterization of the Arg51Gln polymorphism.

DNA Analysis

DNA analysis was performed using the real-time PCR technique with a TaqMan® allelic discrimination probe. The characteristics used are described in the Table 1:

Table 1.

Box 1

Table 1

DNA Analysis conditions

General Conditions	Conditions		Program (50 cycles)			
		Final Volume	Stage	Temperature	Time	Cycles
Polymorphism: rs398123011	2x Master Mix	2.5 uL	Pre incubate	95 ° C	10 min	1
Gene: GHRL Polymorphism: C/T	40x Tub	0.125 uL	Amplification	92° C	15 seg	50
VIC: C (Wild type)	PCR Water	1.875 uL	Extension	60° C	90 seg	1
FAM: T (Polymorphic)	DNA [50 ng/uL)	0.5 uL	Cooling	37 °C	30 seg	1

Statistical Analysis

In this study, descriptive statistics were performed, reporting percentages for qualitative variables, mean and standard deviation for quantitative variables, or median and interquartile range according to distribution. Allelic and genotype frequencies were determined by direct counting of the observed genotypes. The Hardy-Weinberg equilibrium test was performed to verify the study population. The association between variables was assessed using the Chi-square test to determine the Odds Ratio. The relationship between ghrelin serum levels and the dependent variable was analyzed using an ANOVA test. To analyze intervening variables, logistic regression was used. A p-value ≤ 0.05 was considered significant. All data were analyzed using Excel and the statistical package Statgraphics Centurion 19.

Results

Two hundred eighty-nine volunteers were recruited: 94 men and 126 women. They were divided into three groups according to BMI: 97 were of normal weight, 54 were overweight, and 69 were obese. When the polymorphism was characterized, no subject presented the polymorphic allele (T). All volunteers were homozygous for the wild-type allele (C/C).

Study variables were analyzed according to BMI in the three previously mentioned groups. Table (2) shows descriptive data of the population. Ghrelin serum levels were within the normal range (300 – 900 pg/mL). Statistical differences were observed between the normal weight group and the obesity group, with higher levels in the obesity group. It was also observed that the overweight group had a tendency towards lower levels of ghrelin, although this difference was not statistically significant.

We also observed differences in SBP/DBP, triglycerides, and HDL between the overweight and obesity groups compared to the normal weight group, the data is shown in table 2. This could be mainly due to the pattern of adipose tissue accumulation, which is more pronounced in individuals with higher BMI.

Box 2

Table 2

Descriptive data according to BMI

	Normal weight	Overweight	Obesity	p-value
	n=97	n= 54	n= 69	
Ghrelin (pg/mL)	618.5±438.3	481.1±376.5	780.4±444.9*	0.0001
Age (years)	20.3±1.4	21.3±2.1*	21.2±1.7*	0.0001
BMI (Kg/m^2)	21.4±1.9	27.5±1.5*	33.8±4.3*	0.0001
SBP (mm Hg)	109.7±9.8	117.6±10.1	121.6±12.2*	0.0000
DBP (mm Hg)	72.7±8.2	74.6±11.6	79.7±10.3*	0.0001
Triglycerides (mg/dL)	80.8±35.6	116.7±63.3*	140.8±87.5*	0.0001
HDL (mg/dl)	52.3±10.7	41.2±9.9	37.6±10.8*	0.0001

Media ± SD; ANOVA test; post hoc LSD. *Difference respective normal weight group. p<0.05.

Ghrelin serum levels divided into two groups, men and women, are shown in Figure 3. No statistical differences were observed between them.

Box 3

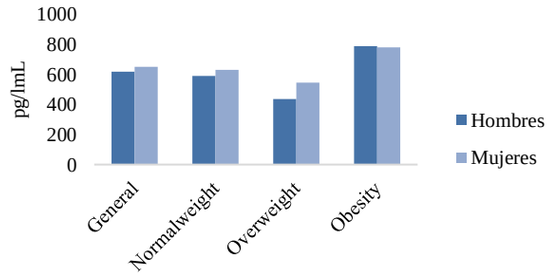


Figure 3

Ghrelin values in men and women

A Chi-square test was conducted to identify if there was an association between ghrelin levels and overweight or obesity, and an association with overweight was found, with an OR of 4.185 and a p-value < 0.0001 (CI 2.105-8.318). The results of all associations are shown in the table 3.

It can be observed that there is an association between ghrelin and overweight when compared to the reference group with normal weight, and even when contrasted with the rest of the volunteers who are not overweight. The OR value is greater than 2 and the results are statistically significant.

Box 4

Table 3

Association of ghrelin with overweight and obesity Descriptive data according to BMI

	Low ghrelin	Normal ghrelin
	Overweight vs Without OW	
OW	23	31
W/OW	25	141
OR	**4.255 (2.105-8.318) p < 0.0001***	
	Overweight/Obesity vs Normal weight	
OW/OB	32	91
NW	16	81
OR	1.780 (0.9102-3.482) p > 0.05	
	Obesity vs Sin Obesity	
OB	9	60
W/O	39	112
OR	0.4786 (0.2233-1.026) p > 0.0547	
	Overweight vs Normal weight	
OW	23	31
NW	16	81
OR	**3.756 (1.755-8.036) p<0.0001**	

*Frequency. OR: Odds ratio (Confident interval). *Significant p<0.05. NW: Normal weight, Ow: Overweight, Ob: Obesity.*

Finally, we conducted a logistic regression to evaluate the role of the intervening variables, shown at table 4. The variable sex was not included in the equation, indicating that it does not influence the ghrelin results. The adjusted OR value for overweight is 4.946 (CI 2.043-11.975) with a p-value < 0.0001.

Box 5

Table 4

Logistic regression to evaluate sex and BMI effect on ghrelin lower levels

Equation variables	B	Wald	Sig.	Exp (B)	CI (95%)
BMI		16.893	0.000		
BMI (1)	.275	.374	.541	1.317	0.545-3.182
BMI (2)	1.599	12.557	0.000	4.946	2.043-11.975
Constant	-1.897	28.167	0.000	0.150	

In addition, complementary analyses of the Arg51Gln genotyping were conducted in a population from western Mexico. A total of 432 individuals from Jalisco (149), Colima (192), and Nayarit (92) were studied. Among these individuals, no polymorphic subjects for Arg51Gln were found, suggesting that this polymorphism might be monomorphic in our population.

Discussion

We observed normal ghrelin levels in the population. When stratified by BMI, lower ghrelin levels were observed in overweight volunteers. Previous studies, such as that by Llamas-Covarrubias et al. (2015), have reported low ghrelin levels in individuals with obesity, but we did not find this in our study. The normal serum ghrelin levels observed in the obese group in our study can be explained in two ways: higher levels of the desacylated form in an attempt to control the energy imbalance, which has been mainly reported in young people; in contrast, reports of low ghrelin levels related to obesity have focused on adults over 40 years old (Akimoto-Takano et al., 2005; Becer & Ergoren 2021).

Another possible reason could be that we are observing an adaptive state where hyperghrelinemia is present, leading to resistance to the positive effects of the hormone due to alterations in receptor binding, receptor expression, or inadequate hormone transport. This could explain why postprandial ghrelin levels do not decrease in obese individuals (Cui et al., 2017). A limitation of this study is that we only measured serum hormone levels and did not measure each isoform or receptor expression. However, our strength lies in our age group, as previous studies have focused on adults who already have more significant metabolic alterations.

We did not find differences in ghrelin levels between men and women. Some studies, such as the one reported by Soriano-Guillén et al. (2016), have suggested that this hormone could exhibit sexual dimorphism. These differences can mainly be explained by variations described in adolescent groups or postmenopausal women. It has been observed that estrogen levels strongly relate to ghrelin synthesis, potentially causing differences not present in our study group.

Regarding the association of ghrelin with overweight, this has been previously described by other authors like Mora et al. (2015). However, they also describe an association of the hormone with obesity.

We only found an association in the overweight group, with an odds ratio greater than 2, indicating that low hormone levels could be considered a risk factor for developing overweight. We believe the lack of association with obesity could be due to an adaptive state by the body. Other studies have shown that once the overweight stage is surpassed, individuals reaching obesity can exhibit metabolic control, leading to what is known as metabolically healthy obesity (MHO). These individuals may have biochemical alterations, such as in lipid profiles, but can still control hormone and cytokine synthesis and secretion, as is the case with ghrelin.

Finding this situation can be advantageous, as we might be dealing with obese individuals who can still return to a healthy metabolic state without severe alterations like insulin resistance. Analyzing other hormones, such as insulin and leptin, could improve our understanding of the findings in this study.

Finally, since no Arg51Gln polymorphism was found in our volunteers, we decided to search in a larger population group with similar sociodemographic characteristics, and no polymorphic subjects were found. This indicates that while we have observed variations in ghrelin levels, they are not due to the presence of a genetic variation, at least not the one described here. Therefore, we might be looking at a population monomorphic for this coding region, opening the door to new questions on this topic.

Conclusions

- The study suggests the possibility of adaptive mechanisms in obese individuals, where normal ghrelin levels might indicate a state of metabolic control, known as metabolically healthy obesity (MHO).
- There were no significant differences in ghrelin levels between men and women within the studied age group.
- The population of western Mexico is monomorphic for the Arg51Gln SNP.
- The lowest ghrelin levels were found in the overweight group, showing statistically significant differences compared to the other groups.
- Low ghrelin levels are associated with overweight but not with obesity.

Declarations

Conflict of interest

The authors declare no interest conflict. They have no known competing financial interests or personal relationships that could have appeared to influence in this chapter.

Author contribution

Uvalle-Navarro, Rosario Lizette: Contributed to conception idea, writing the document, research method and technique.

González-Sandova, Claudia Elena: Contributed to conception idea, writing the document and research method.

Díaz-Burke, Yolanda: Contributed to conception idea and research method.

Mederos-Torres, Claudia Verónica: Contributed to conception idea, writing the document, research method and technique.

Availability of data and materials

Further data is available from the corresponding author on reasonable request.

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Abbreviations

ANOVA	Analysis of Variance
Arg	Arginine
BMI	Body Mass Index
CI	Confidence Interval
DBP	Diastolic Blood Pressure
GH	Growth Hormone
GHRL	Ghrelin gene
GHS-R1a	Growth Hormone Secretagogue Receptor type 1a
GHS-R1b	Growth Hormone Secretagogue Receptor type 1b
Gln	Glutamine
HDL	High-Density Lipoprotein
INSP	National Institute of Public Health
LSD	Least Significant Difference
MHO	Metabolically Healthy Obesity
MS	Metabolic Syndrome
OB	Obesity
OPS	Pan American Health Organization
OR	Odds Ratio
OW	Overweight
PCR	Polymerase Chain Reaction
SNP	Single Nucleotide Polymorphism
SBP	Systolic Blood Pressure
SD	Standard Deviation
W/O	Without Obesity
W/OW	Without Overweight
WHO	World Health Organization

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