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Review Article

Association of *ADIPOQ* Single Nucleotide Polymorphisms (SNPs) with Obesity Risk in Different Populations: A Systematic Review and Analysis

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Abstract

Background: Thirty-two single nucleotide polymorphisms (SNPs) are commonly found in *ADIPOQ*. APN levels are decreased in obesity, and SNPs of the *ADIPOQ* gene affecting APN have varying associations with the development of obesity in different populations. This systematic review and meta-analysis aimed to investigate the association of SNPs in *ADIPOQ* with the risk of obesity development in various populations.

Methods: A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist date up to Feb 2023. We used the Newcastle–Ottawa scale to find out if a study fit the main criteria for submission and to assess the data quality of the articles included in the systematic review and meta-analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated via Review Manager (RM) V.5.4 to estimate the connection between *ADIPOQ* polymorphic qualities of a gene and the risk of developing obesity.

Results: The present study analysed the association between *ADIPOQ* polymorphisms (rs1501299, rs2241766, rs266729, rs822393, and rs822396) and obesity risk and suggested that APN is partially responsible for the emergence of obesity and increases its risk.

Conclusion: It is important to take into account several limitations of this meta-analysis when evaluating the findings. First off, even though we looked through numerous databases for all relevant papers, there is a chance we overlooked some. Our capacity to arrive at more firm conclusions was further hampered by the small number of papers that made up our meta-analysis. The most current data, however, are presented in this study since it used newly published data to perform a meta-analysis and evaluate the relationship between ADIPOQ polymorphisms and obesity.

Keywords: Obesity risk; Single nucleotide polymorphisms; *ADIPOQ* gene

Introduction

Obesity is a multifactorial metabolic disorder characterized by an abnormal accumulation of adipose tissue, leading to an elevated body mass index (BMI) (1). Obesity has emerged as a significant global metabolic problem since the 1970s (2, 3). It is associated with several health issues,

including cardiovascular diseases, metabolic syndrome, type 2 diabetes, and colorectal cancer (4, 5). This rise is attributed to a complex interplay of genetic, environmental, and lifestyle factors. It's not solely a result of overeating or lack of physical activity; genetic predispositions can play a significant role in determining an individual's susceptibility to obesity (6). Understanding the genetic basis of obesity is crucial for developing more effective prevention and treatment strategies. One of the genes that have garnered attention in obesity research is the ADIPOQ gene, which codes for the hormone adiponectin (APN). APN, a hormone secreted by the adipose tissue, is responsible for fat synthesis and is encoded by the *ADIPOQ* gene (7).

Being overweight or obese is a serious global public health issue and the fifth biggest risk factor for deaths worldwide (8). Overaccumulation of visceral adipose tissue has been identified as a major driving factor for type 2 diabetes (9). By secreting adipokines, the adipose tissue plays a significant role in regulating metabolic balance. The adipokine APN, which is generated by adipocytes, has anti-inflammatory and insulin-sensitizing qualities (10). Numerous prospective studies have linked a decreased incidence of diabetes to high levels of circulating APN.

Low molecular weight (LMW), moderate molecular weight (MMW), and high molecular weight (HMW) are the three polymorphic variants of APN that are in circulation (11). It's interesting that plasma glucose levels and the ratio of plasma HMW APN to total APN associated more strongly than with any of the other forms. Strong connections have been observed between the APN gene (ADIPOQ/APM1/GBP 28) locus 3q27 and a number of metabolic diseases, including type 2 diabetes, dyslipidemia, obesity, and poor glucose tolerance. Its SNPs also have a strong correlation with obesity.

Obesity affects various cell types in different tissues, particularly pancreatic β-cells, kidneys, and heart, and regulates the genes responsible for liver glucogenesis. Additionally, APN improves insulin sensitivity by affecting primary metabolic tissues and overall energy homeostasis of the body (12).

The *ADIPOQ* gene encodes APN and is located at the chromosomal locus 3q27. It consists of 244 amino acids and contains three exons and two introns (13). Thirty-two single nucleotide polymorphisms (SNPs) are commonly found in *ADIPOQ* (14). APN levels are decreased in obesity, and SNPs of the *ADIPOQ* gene affecting APN have varying associations with the development of obesity in different populations. With the escalating global burden of obesity and its associated comorbidities, elucidating the genetic factors contributing to its development is of importance.

This systematic review and meta-analysis aimed to investigate the association of SNPs in *ADIPOQ* with the risk of obesity development in various populations.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (20) was followed in conducting the systematic review. The following were the requirements for qualifying in the source studies:

Inclusion criteria

- Case-control studies
- Studies that looked into the association between SNPs of the *ADIPOQ* gene and the possibility of developing obesity in different people
- Researches that provided information on genotypes and allele frequencies

Exclusion criteria

- Systematic reviews, meta-analyses, and repeated studies- Articles that did not examine the association between *ADIPOQ* polymorphisms and risk of obesity development
- Studies in which it was not possible to determine whether the control population was in Hardy–Weinberg equilibrium

Articles were searched by published date up to Feb 2023 in PubMed, Google Scholar, Web of

Science, and Cochrane Library databases using the terms "obesity", "adiponectin", "ADIPOQ", "SNP", and "polymorphism". Based on the search results, only human-based articles were selected. Two authors independently selected the search results based on the eligibility criteria. The collected studies were entered into Rayyan. After removing duplicate articles, the remaining articles' titles and abstracts were scrutinized.

The following data were extracted from the selected articles: first author's name, year of publication, population ethnicity, number of cases and controls, and genotype frequency. One author conducted data collection and analysis.

Risk of bias

To determine whether a study met the inclusion criteria and to assess the data quality of the articles included in the systematic review and meta-analysis, the Newcastle–Ottawa scale was used. The articles were assessed independently by two researchers to determine the quality of nonrandomised studies. The results of the examination were discussed, and articles were selected based on their scores on the Newcastle–Ottawa scale (15). The total scores ranged from zero to nine, with scores above six indicating high quality (Table 1).

Table 1: Newcastle-Ottawa scale

Study	***Selection***				***Comparability***		***Exposure***	***Total***
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for the most important factor	Study controls for any additional factors	Assertainment of the exposure (max of 2 stars)	
Beebe-Dimmer (16)	*	*	*	*	*	*	**	8
De Luis (17)	*	*	*	*	*	*	**	8
Boumaiza (18)	*	*	*	*	*		**	7
Elghazy (19)	*	*	*	*	*		**	7
Hsiao (20)	*	*	*	*	*	*	**	8
Kaur (21)	*	*	*	*	*	*	**	8
Ramya (22)	*	*	*	*	*	*	**	8
Romero (23)	*	*	*	*	*	*	**	8
Vankova (24)	*	*	*	*	*		**	7
Zaki (25)	*	*	*	*	*		**	7
Zayani (26)	*	*	*	*	*		**	7

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using Review Manager (RM) v. 5.4 to estimate the relationship between *ADIPOQ* gene polymorphisms and the risk of obesity. The pooled OR was performed for the domi-

nant, recessive, and over-dominant models. The Chi-square-based Q and I-squared tests were used to analyse heterogeneity (P<0.10). Heterogeneity between studies was evaluated using the I2 test: when I2 was <50%, the fixed-effects model was used; if I2 was > 50% to 90%, a random-effects model was used. Publication bias was assessed using a funnel plot. Review Manager ver. 5.4 was used to perform all the analyses and calculations.

OR = 1 Exposure does not affect odds of outcome

OR > 1 Exposure associated with higher odds of outcome

OR < 1 Exposure associated with lower odds of outcome

The CI value estimates the precision of the OR value. However, unlike the P-value, the 95% CI does not report a measure's statistical significance, as a small CI indicates a higher precision of the OR.

Results

To investigate the association of SNPs of the ADIPOQ gene with the risk of obesity development, here were matches between 1540 PubMed articles, 30 Cochrane Library articles, 31 Web of Science database items, and 4500 Google Scholar articles, including 600 research results. First, 136 articles were selected from the databases by analysing their titles and abstracts. During the secondary examination, articles that did not meet the eligibility criteria were reduced, including 87 articles that did not show an association between polymorphisms and obesity, 31 that did not show genotype frequency, and 18 that were not case-control studies (Fig. 1).

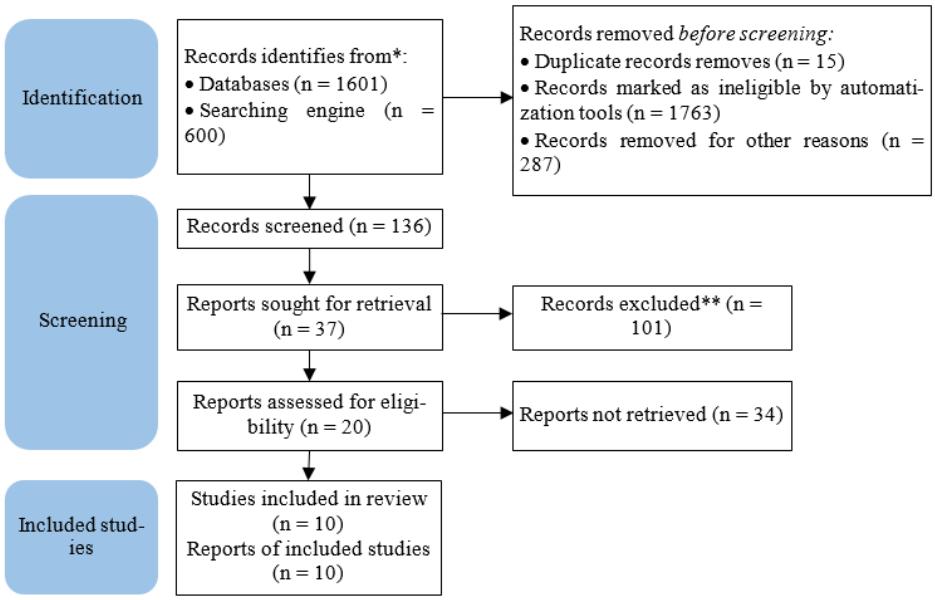

Fig. 1: Flowchart of study selection

rs1501299 polymorphism and obesity risk

Nine studies (7, 8, 9, 15, 16, 17, 18, 20, 23) were analysed to determine the association between the rs1501299 polymorphism and obesity risk. There were no significant associations between rs1501299 and obesity under dominant (OR=0.77, 95% CI=0.56–1.07), recessive (OR=0.66, 95% CI=0.47–0.92), and over-dominant (OR=0.95, 95% CI=0.70–1.28) genetic models. However, in the subgroup analysis, the Tunisian population showed a significant association with obesity risk under the dominant model (OR=1.65, 95% CI=1.28–2.14) (Table 2).

Table 2: Main characteristics of included studies, distribution of genotypes and subgroup analysis of rs1501299

Population	*Author*	*Year*	*Sample size*	*GG*		*GT*		*TT*		*Dominant comparison*	*Recessive comparison*	*Over-dominant comparison*
				Obese	Control	Obese	Control	Obese	Control	GG vs GT+TT	GG+GT vs TT	GT vs GG+TT
Punjabi	Kaur (21)	2018	250/300	140	185	66	81	44	34	0.79(0.56-1.11)	0.60(0.37-0.97)	0.97(0.66-1.42)
Egyptian	Elghazy (19)	2019	100/97	16	52	38	37	43	11	0.18(0.09-0.35)	0.16(0.07-0.33)	1.10(0.62-1.95)
French	De Luis (17)	2006	1229/1350	545	688	457	488	91	79	0.82(0.70-0.96)	0.74(0.54-1.01)	1.13(0.96-1.33)
Tunisian	Zayani (26)	2016	721/400	156	201	136	397	108	123	1.65(1.28-2.14)	0.56(0.41-0.75)	0.42(0.33-0.54)
African-american	Beebe-Dimmer (16)	2010	131/344	37	100	45	97	19	25	0.71(0.43-1.14)	0.55(0.29-1.05)	1.04(0.64-1.66)
Tunisian	Boumaiza (18)	2011	160/169	97	88	54	60	9	21	1.42(0.91-2.20)	2.38(1.06-5.37)	0.93(0.59-1.46)
South Indian	Ramya (22)	2013	1100/1100	552	667	242	206	24	22	0.71(0.58-0.87)	0.83(0.46-1.50)	1.41(1.13-1.74)
Egyptian	Zaki (25)	2014	104/100	2	15	45	44	57	41	0.11(0.02-0.50)	0.57(0.33-1.00)	0.97(0.56-1.69)
Bulgarian	Vankova (24)	2014	67/97	35	47	25	36	7	13	1.14(0.61-2.13)	1.34(0.51-3.57)	0.99(0.52-1.89)

rs2241766 and obesity risk

Six studies (7, 8, 15, 17, 18, 22) were analysed to determine the association between the rs2241766 polymorphism and risk of obesity. There were no significant associations under dominant (OR=0.85, 95% CI=0.67–1.08) and recessive (OR=0.84, 95% CI=0.69–1.01) models. Association with obesity risk was observed under the over-dominant model (OR=1.05, 95% CI=0.94–1.18), especially in the Tunisian population (OR=1.68, 95% CI=0.94–3.01) (Table 3).

Table 3: Main characteristics of included studies, distribution of genotypes and subgroup analysis of rs2241766

Population	*Author*	*Year*	*Sample size*	*TT*		*TG*		*GG*		*Dominant comparison*	*Recessive comparison*	*Over-dominant comparison*
				Obese	Control	Obese	Control	Obese	Control	TT vs TG+GG	TT+TG vs GG	TG vs TT+GG
Egyptian	Elghazy (19)	2019	100/97	251	443	123	244	26	34	1.06(0.82-1.36)	0.71(0.42-1.20)	0.87(0.67-1.13)
Tunisian	Zayani (26)	2016	721/400	16	52	38	37	31	25	0.28(0.14-0.53)	0.49(0.26-0.92)	1.68(0.94-3.01)
African-American	Beebe-Dimmer (16)	2010	131/344	93	204	10	21	0	0	0.96(0.43-1.21)	Not estimable	1.04(0.47-2.31)
French	De Luis (17)	2006	1229/1350	841	957	270	275	23	26	0.90(0.75-1.09)	1.02(0.58-1.80)	1.12(0.92-1.35)
Tunisian	Boumaiza (18)	2011	160/169	104	105	48	56	8	8	1.13(0.72-1.77)	0.94(0.35-2.58)	0.86(0.54-1.38)
Mexican	Romero (23)	2015	724/745	189	225	350	349	168	161	0.83(0.66-1.04)	0.90(0.70-1.15)	1.08(0.88-1.33)

rs266729 and obesity risk

Six studies (7, 8, 15, 17, 18, 23) were analysed to determine the association between rs266729 polymorphism and obesity risk. rs266729 showed a significant association with obesity risk among other *ADIPOQ* polymorphisms and genetic models (OR=1.15, 95% CI=0.91–1.45) under the dominant genetic model. Association with obesity risk under the dominant model was detected for the Egyptian population (OR=3.55, 95% CI=1.89–6.67) (Table 4).

rs822393 and obesity risk

Data from the three studies (7, 8, 17) were analysed to determine the association between rs822393 and the risk of obesity. After pooling the data, a strong association with obesity risk was identified in the over-dominant genetic model (OR = 1.29, 95% CI = 0.97–1.70). However, other two genetic models did not show association with obesity risk (recessive comparison: OR = 0.99, 95% CI = 0.83–1.19; dominant comparison: OR = 0.78, 95% CI = 0.65–0.95). In the subgroup analysis, the Tunisian population showed a strong association with obesity development risk under the over-dominant model (OR = 1.77, 95% CI = 1.38, 2.27) (Table 5).

Table 4: Main characteristics of included studies, distribution of genotypes and subgroup analysis of rs266729

Population	*Author*	*Year*	*Sample size*	*CC*		*CG*		*GG*		*Dominant comparison*	*Recessive comparison*	*Over-dominant comparison*
				Obese	Control	Obese	Control	Obese	Control	CC vs CG+GG	CC+CG vs GG	CG vs CC+GG
Egyptian	Elghazy (19)	2019	100/97	77	52	18	44	2	4	3.55(1.89-6.67)	1.98(0.35-11.06)	0.29(0.15-0.55)
African-american	Beebe-Dimmer (16)	2010	131/344	104	248	24	62	3	4	1.03(0.62-1.69)	0.55(0.12-2.49)	0.91(0.54-1.54)
French	De Luis (17)	2006	1229/1350	713	704	435	524	64	98	1.26(1.08-1.48)	1.43(1.03-1.98)	0.86(0.73-1.01)
South Indian	Ramya (22)	2011	1100/1100	521	670	326	485	49	67	1.14(0.96-1.36)	1.00(0.69-1.46)	0.87(0.73-1.04)
Mexican	Romero (23)	2015	724/745	253	289	346	347	112	97	0.85(0.69-1.05)	0.82(0.61-1.09)	1.05(0.86-1.30)
Taiwanese	Hsiao (20)	2016	388/663	129	463	88	289	20	58	0.90(0.67-1.20)	0.84(0.49-1.42)	1.06(0.79-1.44)

Table 5: Main characteristics of included studies, distribution of genotypes and subgroup analysis of rs822393

Population	*Author*	*Year*	*Sample size*	*CC*		*CT*		*TT*		*Dominant comparison*	*Recessive comparison*	*Over-dominant comparison*
				Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	CC vs CG+GG	CC+CG vs GG	CG vs CC+GG
Mexican	Romero (23)	2015	724/745	189	225	350	349	168	161	0.83(0.66-1.04)	0.90(0.70-1.15)	1.08(0.88-1.33)
Tunisian	Zayani (26)	2016	721/400	173	394	195	252	32	75	0.63(0.49-0.81)	1.34(0.87-2.06)	1.77(1.38-2.27)
South Indian	Ramya (22)	2011	1100/1100	418	601	340	425	67	90	0.88(0.73-1.05)	0.99(0.71-1.38)	1.14(0.95-1.37)

rs822396 and obesity risk

Three studies (7, 8, 19) were analysed to determine the association between rs822396 and obesity risk. Higher association with obesity risk was observed under the over-dominant model (OR=1.07, 95% CI=0.92–1.24) in comparison with the dominant (OR=0.85, 95% CI=0.73–0.99) and recessive models (OR=0.84, 95% CI=0.69–1.01). In subgroup analysis, high OR was observed in the African-American population under the recessive model (OR=2.34, 95% CI=0.50–10.87) (Table 6).

Table 6: Main characteristics of included studies, distribution of genotypes and subgroup analysis of rs822396

Population	*Author*	*Year*	*Sample size*	*AA*		*AG*		*GG*		*Dominant comparison*	*Recessive comparison*	*Over-dominant comparison*
				Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	CC vs CG+GG	CC+CG vs GG	CG vs CC+GG
Punjabi	Kaur (21)	2018	250/300	114	148	105	134	31	18	0.86(0.61-1.21)	0.45(0.25-0.83)	0.90(0.64-1.26)
African-american	Beebe-Dimmer (16)	2010	131/344	70	139	32	79	2	10	1.32(0.81-2.15)	2.34(0.50-10.87)	0.84(0.51-1.38)
South Indian	Ramya (22)	2011	1100/1100	355	540	400	495	107	120	0.80(0.67-0.95)	0.82(0.62-1.08)	1.15(0.97-1.38)

Discussion

Adipose tissue secretes plasma APN, with *ADIPOQ* being the only significant gene expressing it. The increased phosphorylation and activity of AMP-activated protein kinase and peroxisome proliferator-activated receptor-α activity are believed to be mediated by APN, which binds to APN receptors (AdipoR1 and AdipoR2) to activate glucose uptake and fatty acid oxidation in both skeletal and cardiac muscles (7). APN replacement in humans is a promising strategy for treating and preventing type 2 diabetes and obesity. APN-deficient animals show signs of insulin resistance (8, 29). Individuals with obesity had lower plasma APN levels compared to lean patients, and that weight loss could considerably raise these levels. The present study analysed the association between *ADIPOQ* polymorphisms (rs1501299, rs2241766, rs266729, rs822393, and rs822396) and obesity risk and suggested that APN is involved in the development of obesity and increases its risk (Table 7). Previous studies have reported potential roles of other APN polymorphisms of genes in patients who have diabetes of the second type and obesity. The association between rs1501299 and rs266729 polymorphisms of ADIPOQ gene, and type 2 diabetes mellitus in an Iranian population was analysed (27). By looking at the results we can determine that the APN polymorphism of rs266729 gene with SNP − 11,377 C > G is strongly connected with the risk of obesity in the population of Iran; however, the same was not observed for the rs1501299 (SNP + 276 G > T) polymorphism. We noticed the same tendency for *ADIPOQ* rs1501299, which was strongly correlated with obesity in Caucasians (9) but not in Nigerians (25). However, this meta-analysis suggests that the *ADIPOQ* rs266729 polymorphism is most significantly associated with obesity and its risk of development.

Although obesity is ubiquitous, research has shown prevalence patterns based on ethnicity and SNPs (8). For instance, in the population of Mexico, the only gene to show a protective association with obesity was rs11061971 of *ADIPOQ2*, and there was no correlation noticed between the rs2241766 polymorphism of *ADIPOQ* and obesity (28, 29). In contrast, studies have established that the rs2241766 polymorphism is associated with obesity in the Chinese population (7, 30).

While this study provides valuable insights into the association between ADIPOQ polymorphisms and obesity risk, it is important to consider several limitations of this meta-analysis when evaluating the findings. First off, even though we looked through numerous databases for all relevant papers, there is a chance we overlooked some. Our capacity to arrive at more firm conclusions was further hampered by the small number of papers that made up our meta-analysis.

Table 7: Pooled ORs and 95% CIs of the associations between ADIPOQ SNPs and obesity risk

Polymorphism	*Total*	*Heterogeneity*	*Dominant model P-value OR (95%CI)*	*Recessive model P-value OR (95%CI)*	*Over-dominant model P-value OR (95%CI)*
rs1501299	3090/3858	Dominant: I^2 = 87% Recessive: I^2 = 73% Over-dominant: I^2 = 86%	0.77 [0.56, 1.07]	0.66 [0.47, 0.92]	0.95 (0.70-1.28)
rs2241766	2589/3222	Dominant: I^2 = 68% Recessive: I^2 = 1% Over-dominant: I^2 = 13%	0.85 [0.67, 1.08]	0.84 [0.69, 1.01]	1.05 (0.94-1.18)
rs266729	3284/4505	Dominant: I^2 = 79% Recessive: I^2 = 39% Over-dominant: I^2 = 68%	1.15 [0.91, 1.45]	1.02 [0.85, 1.21]	0.87 (0.72-1.06)
rs822393	1932/2572	Dominant: I^2 = 57% Recessive: I^2 = 17% Over-dominant: I^2 = 81%	0.78 [0.65, 0.95]	0.99 [0.83, 1.19]	1.29 (0.97-1.70)
rs822396	1216/1683	Dominant: I^2 = 44% Recessive: I^2 = 61% Over-dominant: I^2 = 25%	0.85 [0.73, 0.99]	0.75 [0.41, 1.36]	1.07 (0.92-1.24)

The most current data, however, are presented in this study since it used newly published data to perform a meta-analysis and evaluate the relationship between ADIPOQ polymorphisms and obesity.

Despite this limitation, the study possesses several notable strengths that contribute to its significance. Firstly, this study offers a comprehensive analysis of the relationship between ADIPOQ polymorphisms and obesity risk. Furthermore, the study employs various genetic models, including dominant, recessive, and over-dominant models, to assess the association between ADIPOQ polymorphisms and obesity risk. Lastly, the study's focus on specific ADIPOQ polymorphisms (e.g., rs1501299, rs2241766, rs266729) narrows its scope and allows for a more targeted investigation of the genetic variants affecting obesity risk. These results advance understanding of the genetic underpinnings of obesity and contribute valuable insights to the field of genetic epidemiology.

Conclusion

The findings of this analysis underscore the complexity of genetic factors contributing to obesity and emphasize the importance of exploring specific genetic variants.

The present study analysed the association between *ADIPOQ* polymorphisms (*rs1501299, rs2241766, rs266729, rs822393,* and *rs822396*) and

obesity risk and suggested that APN raises the risk of obesity and contributes to its development.

One potential perspective is the development of more personalized approaches to obesity prevention and management. Understanding how specific *ADIPOQ* polymorphisms influence obesity risk can lead to tailored interventions and treatments based on an individual's genetic profile.

Additionally, as genetic data becomes more accessible and affordable, larger-scale studies with diverse populations can be conducted to validate and extend the current findings. Collaborative efforts across multiple research institutions can enhance the robustness and generalizability of genetic associations.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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