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Genetic etiology and clinical features of non-syndromic pediatric obesity in the Chinese population: a large cohort study

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Abstract

Background This study aimed to investigate the genetic etiology and clinical features of non-syndromic pediatric obesity in a large Chinese cohort, providing insights into the genetic profile and its correlation with clinical phenotypes.

Methods We enrolled 391 children, aged 7–14 years, diagnosed with non-syndromic pediatric obesity at Jiangxi Provincial Children's Hospital from January 2020 to June 2022. Whole-exome sequencing was employed to identify potential genetic causes, focusing on 79 candidate genes associated with obesity. Multivariate logistic regression analysis was performed on the clinical data of the non-syndromic obesity gene-positive group and the gene-negative group.

Results Among the 391 patients, 32 (8.2%) carried 18 non-syndromic obesity genes, with UCP3 and MC4R being the most common. Seven cases (1.8%) were rated as likely pathogenic by the American College of Medical Genetics and Genomics (ACMG). Clinical phenotype and genetic correlation analysis revealed that urinary microalbumin, fT4, GGT, uric acid, serum phosphorus, paternal weight, family history, impaired glucose tolerance (IGT), non-HDL cholesterol (non-HDL-C), and metabolic syndrome (MetS) showed significant statistical differences ($P < 0.05$). Serum phosphorus is an independent risk factor associated with genetic predispositions to obesity in children and adolescents ($P < 0.05$).

Conclusion Our findings highlight the genetic heterogeneity of non-syndromic pediatric obesity and identify UCP3 and MC4R as potential hotspot genes in the Chinese population. The study underscores the potential of genetic testing for early diagnosis and personalized management of pediatric obesity.

Keywords Non-syndromic obesity, MC4R, UCP3, Whole-exome sequencing, Pediatric obesity

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Background

Pediatric obesity is a serious and urgent public health issue faced globally. Over the past decade, the prevalence of obesity among children and adolescents has increased at an alarming rate. An epidemiological survey of 128.9 million children and adolescents worldwide [1] showed that the prevalence of obesity reached 5.6% in 2016. The PRODY study, conducted from 2017 to 2019 on 201,098 Chinese children and adolescents aged [2], revealed that the overall prevalence of obesity among Chinese children and adolescents is 8.9%.

Monogenic obesity typically manifests in early childhood and is primarily associated with genes involved in the leptin-melanocortin pathway, leading to hypothalamic dysregulation of hunger and satiety. Unlike common obesity, monogenic obesity is rare and characterized by severe early-onset obesity, usually occurring before the age of 10, and accounts for approximately 5% of severe early-onset obesity cases.

To date, there have been no large-scale genetic etiology studies on non-syndromic obesity in the Chinese population. Therefore, this study conducts whole-exome sequencing on 391 children with non-syndromic obesity to obtain a genetic profile of non-syndromic obesity in the Chinese population and to analyze the correlation with clinical phenotypes.

Methods

Study setting and recruitment

This study encompassed patients diagnosed with obesity who were admitted to Jiangxi Provincial Children's Hospital, from January 2020 to December 2022. This study was approved by the Medical Ethics Committee of the Jiangxi Provincial Children's Hospital (Approval No. JXSETYY-YXKY–20190003) and all participants provided written informed consent. Clinical trial number: Not applicable. Written informed consent was obtained from individual or guardian participants.

Inclusion and exclusion criteria

Clinical data of 400 patients with obesity who visited the Department of Endocrinology and Genetic Metabolism at Jiangxi Provincial Children's Hospital from January 2020 to December 2022 were retrieved from the electronic medical record system.

The data included 9 cases were excluded according to the exclusion criteria, 3 cases were short stature (height below the 5th percentile), 1 case has hypophyseal stalk blocking syndrome, 5 cases have mental retardation, and 391 non-syndromic patients with obesity were finally included.

Inclusion Criteria: (1) Age between 7 and 14 years, with the onset of obesity occurring before the age of 10; (2) Screening and diagnostic criteria were based on the 2018 Health Industry Standard of the People's Republic of China, "Overweight and Obesity Screening in School-Age Children and Adolescents" [3], and the 2022 "Expert Consensus on the Diagnosis, Assessment, and Management of Childhood Obesity in China" [4].

Exclusion Criteria: (1) Patients with obesity and syndromic conditions, such as short stature (height below the 5th percentile), intellectual disability, hearing abnormalities, congenital retinal abnormalities, poor gonadal development, thyroid dysfunction, skeletal deformities, autism, etc.; (2) Patients with obesity who had previously undergone genetic testing with a clear etiology; (3) Patients with obesity who had taken medications that promote appetite or weight gain; (4) Children who refused to participate in this study.

Data collection and measurement

Participant characteristics

Pediatricians in the endocrinology department performed all the anthropometric and blood pressure measurements. A mercury sphygmomanometer was used to measure systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP; mmHg) in the right upper arm after resting for at least 10 min. Blood pressure was assessed three times at 2-minute intervals, and the mean of these three measurements was calculated.

Patient clinical data, including the initial age of obesity onset, age at visit, height, weight, Body mass index (BMI; the weight in kilograms divided by the square of the height in meters), waist circumference, hip circumference, history of overeating eating, family history of Obesity, hypertension and diabetes, blood pressure, physical examination.

Laboratory tests

Venous blood samples were collected in the morning following an overnight fast. Each samples was promptly processed, stored in a refrigerated state, and subsequently transported to the clinical laboratory at Jiangxi Provincial Children's Hospital for immediate analysis. All clinical analyses were conducted in our laboratory, which holds certification from the China National Accreditation Service for Conformity Assessment.

The levels of serum insulin, C-peptide, and 25-hydroxyvitamin D (25(OH)D) were determined using the automated chemiluminescence immunoassay analyzer (Mindray CL–6000i, China). Serum concentrations of general biochemistry tests, including free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), and Testosterone (T), were measured with the UniCel DxI 800 Access analyzer (Beckman Coulter Inc., USA). Triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma

glucose, alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, and phosphorus were quantified using the AU5800 Full-automatic biochemical analyzer (Beckman Coulter Inc., USA).The concentrations of serum insulin-like growth factor−1 (IGF−1) and insulin-like growth factor binding protein−3 (IGF-BP3) were determined using the Immulite 2000 XPi analyzer (Siemens Healthcare Diagnostics, USA). Glycated hemoglobin (HbA1c) levels were measured with the MQ6000 Hemoglobin A1c Analyzer (China). Hypertriglyceridemia (TG) is characterized by levels ≥ 1.47 mmol/L. The BA400 specific protein analyzer was utilized for the detection of urinary microalbumin.

All participants underwent a 75-g oral glucose tolerance test (OGTT; 1.75 g per kg, maximum 75 g), with blood samples drawn at 0, 30, 60, 90, and 120 min for glucose, insulin, and C-peptide measurements.The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) = fasting plasma glucose (FPG, mmol/L) × fasting insulin (FINS, μU/mL) / 22.5.

Whole exome sequencing

1) **DNA library Preparation:** Genomic DNA was extracted from peripheral blood using the QIAamp DNA Mini Kit (Qiagen, Shanghai, China) using the manufacturer's instructions. The DNA was quantified with Nanodrop 2000 (Thermal Fisher Scientific, USA). Genomic DNA of 1–3 μg was fragmented to an average size of 150 bp using a S220 Focusedultrasonicator (Covaris, Massachusetts, USA). A DNA Sample Prep Reagent Set (MyGenostics, Beijing, China) was used for the preparation of standard libraries, including end repair, adapter ligation, and PCR amplification, which would be further sequenced by DNBSEQ (DNBSEQ-T7).
2) **Enrichment and Sequencing of Targeted Genes:** The amplified DNA was captured using Whole Exome Sequencing kit (MyGenostics Inc, Beijing, China). The biotinylated 100 bp capture probes were designed to tile along the coding exons plus 50 bp flanking regions of all the genes. The capture experiment was conducted according to manufacturer's protocol. Briefly, DNA library of 500ng was mixed with Buffer BL and GenCap gene panel probes (MyGenostics Inc), firstly. The mixture was heated at 9 for 5 min, and then 65 for 5 min on a PCR machine. After that, 19 μl of the 65 prewarmed Buffer HY (MyGenostics, MD, USA) was added into the mixture, and this mixture was held at 65 with PCR lid heat on for 16–24 h for hybridization. 50 μl of MyOne beads (Life Technology) was washed using 50 μl of 1X binding buffer for 3 times, and then they were resuspended in 50 μl of 1X binding buffer. The hybrid mixture. Then, beads were washed with WB1 buffer at room temperature for 15 min once, and WB3 buffer at 65 °C for 10 min three times. The bounded DNA was eluted with buffer, and amplified for 13 cycles using the following program: 95 °C for 4 min s (1 cycle); 98 °C for 30 s, 65 °C for 30 s, 72 °C for 30 s (13 cycles); 72 °C for 5 min (1 cycle). The PCR product was purified using SPRI beads (Beckman Coulter) according to manufacturer's protocol. The enrichment libraries were sequenced on DNBSEQ (DNBSEQ-T7). sequencer for paired-reading of 150 bp.
3) **Bioinformatics analysis:** After sequencing, the raw data were saved as a FASTQ format. Both MGI sequencing adapters and low quality reads (< 80 bp) were filtered by cutadaptor software (http://code.google.com/p/cutadapt/). The clean reads were mapped to the UCSC hg19 human reference genome using the parameter BWA of Sentieon software.(https://www.sentieon.com/). The duplicated reads were removed using the parameter driver of Sentieon software, and the parameter driver is used to correct the base, so that the quality value of the base in the reads of the final output BAM file can be closer to the real probability of mismatch with the reference genome, and the mapped reads were used for the detection of variation. The variants of SNP and InDel were detected by the parameter driver of Sentieon software. Then, the data would be transformed to VCF format. Variants were further annotated by ANNOVAR software (http://annovar.openbioinformatics.org/en/latest/), and associated with multiple databases, such as, 1000 genome, ESP6500, dbSNP, EXAC, Inhouse (MyGenostics), HGMD, and also predicted by SIFT, PolyPhen−2, MutationTaster, GERP++.
4) **The whole genome CNV analysis:** The whole genome Copy Number Variation (CNV) analysis obtains FASTQ format based on the above methods, and the sequencing adapters and low quality reads were filtered by cutadaptor software (http://code.google.com/p/cutadapt/). The clean reads were mapped to the UCSC hg19 human reference genome using the parameter BWA of Sentieon software.(https://www.sentieon.com/). Then, CNVkit (https://cnvkit.readthedocs.io/en/stable/) software was used to obtain copy number variation information.

5) **Variants Selected:** In this study, four steps were used to select the potential pathogenic mutations in downstream analysis: (i) Mutation reads should be more than 5, and mutation ration should be no less than 30%; (ii) The mutations should be removed, when the frequency of mutation was more than 5% in 1000 g, ESP6500, and Inhouse database; (iii) The mutations should be dropped, if they were in InNormal database (MyGenostics); (iV) The synonymous mutations should be removed, when they were not Genetic Variation Data Analysis.in the HGMD database. After that, the rest mutations should be the potential pathogenic mutations for further analysis.
6) **Genetic variation screening:** The pathogenicity analysis was conducted using the American College of Medical Genetics and Genomics (ACMG) standards and guidelines [5]. Secondary data analysis was performed on the 79 candidate genes which were selected following a comprehensive literature review [6–11](ADCY3, AFF4, ALMS1, ARL6, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BDNF, CEP290, CFAP418, CPE, CREBBP, CUL4B, DNMT3A, DYRK1B, EP300, GNAS, HTR2C, IFT172, IFT27, IFT74, INPP5E, ISL1, KIDINS220, KSR2, LEP, LEPR, LZTFL1, MAGEL2, MC3R, MC4R, MECP2, MKKS, MKS1, MRAP2, NCOA1, NR0B2, NRP1, NRP2, NTRK2, PCNT, PCSK1, PHF6, PHIP, PLXNA1, PLXNA2, PLXNA3, PLXNA4, POMC, PPARG, PROK2, RAB23, RAI1, RPGRIP1L, RPS6KA3, SDCCAG8, SEMA3A, SEMA3B, SEMA3C, SEMA3D, SEMA3E, SEMA3F, SEMA3G, SH2B1, SIM1, TBX3, TRIM32, TRPC5, TTC8, TUB, UCP3, VPS13B, WDPCP).
A total of 1859 sites (MAF ≤ 0.02) were selected from the data of the 79 reported obesity candidate genes. After manual quality control filtering, 1498 remained (Ratio ≥ 0.25, Depth ≥ 10, Mutcount > 5). Variants with clear pathogenicity were selected, and variants of unknown significance with a Bayesian score greater than 2 were also selected [12]. Variants rated as pathogenic(P) or likely pathogenic(LP) by ACMG, combined with the children's clinical phenotypes, were included in the final diagnosis; those rated as uncertain significance (VUSs), with a Bayesian score ≥ 2, were also included in the final analysis after clinical phenotype analysis (Fig. 1). The pathogenicity of variants was scored using Polyphen−2, SIFT, and MutationTaster.

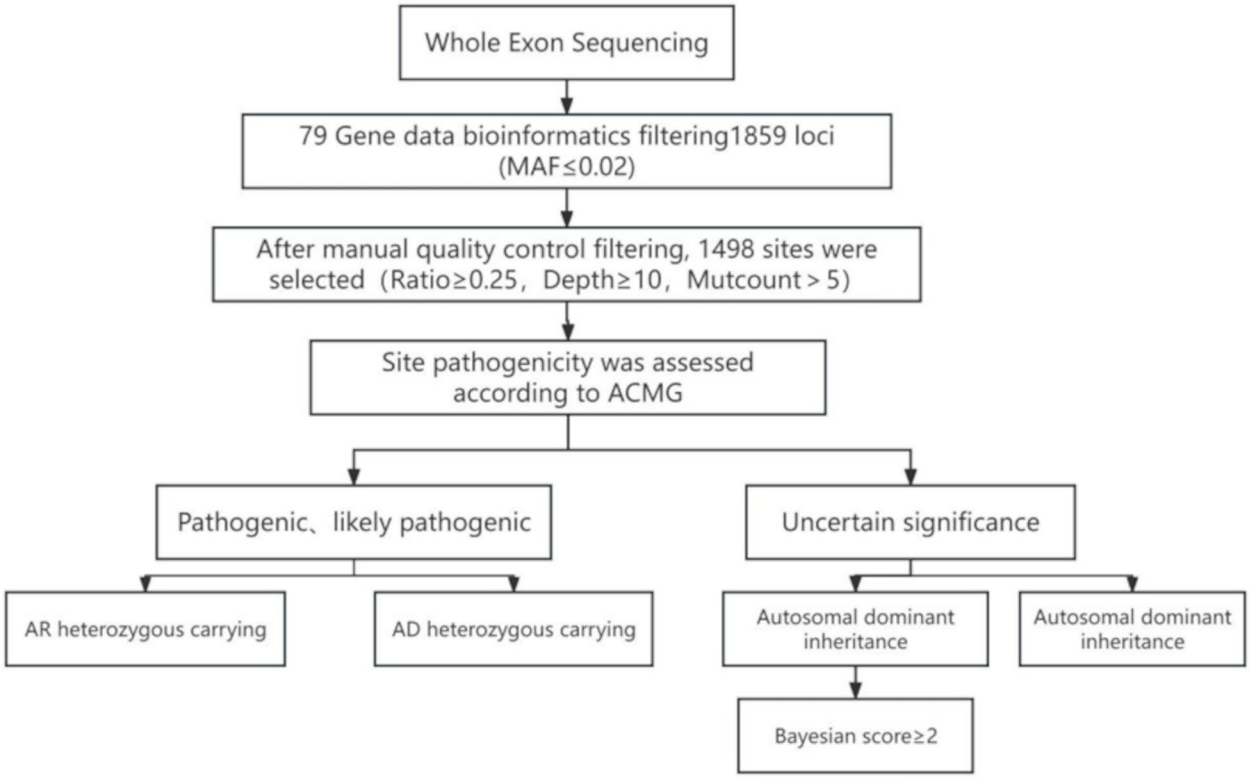

Fig. 1 Screening strategies for obesity gene variants

Statistical analysis

The Height-for-age z-scores and BMI-for-age z-scores were determined using the WHO AnthroPlus software version 1.0.4 (for children above five) (World Health Organization 2009). The z-scores of the abovementioned growth indicators were interpreted according to the recommendations of the World Health Organization(https://www.who.int/tools/growth-reference-data-for–5to19-year).Data were analyzed using IBM SPSS statistics version 22.0 (IBM Corp, Armonk, NY). For continuous variables exhibiting a normal distribution, the mean ± standard deviation (SD) was reported; for those with a skewed distribution, the median and interquartile range (IQR) were utilized. Differences between the two groups were assessed using either the independent samples t-test or the Mann-Whitney U test, depending on the distribution of the data. Categorical variables are presented as [example (%)]. The Pearson chi-square test, the continuous correction chi-square test, or Fisher's exact test were employed to compare categorical differences between the groups. Multivariate logistic regression analysis was performed to identify risk factors and to develop a corresponding nomogram model.

Software and Database.

Sentieon: https://www.sentieon.com/.
CNVkit: https://cnvkit.readthedocs.io/en/stable/.
ANNOVAR: http://annovar.openbioinformatics.org/en/latest/.
1000 genome: http://www.1000genomes.or/.
EVS: http://evs.gs.washington.edu/EVS.
dbSNP: http://www.ncbi.nlm.nih.gov/projects/SNP/.
EXAC: http://exac.broadinstitute.org/.
HGMD: http://www.biobase-international.com/product/hgmd.
SIFT: http://sift.jcvi.org/.
PolyPhen–2: http://genetics.bwh.harvard.edu/pph2/.
MutationTaster: http://www.mutationtaster.org/.
GERP++: http://mendel.stanford.edu/SidowLab/downloads/gerp/index.html.
SPIDEX: http://www.deepgenomics.com/spidex.

Results

General clinical data analysis

Among these 391 patients, there were 301 boys and 90 girls, resulting in a male-to-female ratio of 3.35:1, indicating that the proportion of boys was significantly higher than that of girls.The median age of the subjects at the time of visit was 10.35 ± 1.73 years (range: 7–14 years), the median height was 147.56 ± 11.13 cm (range: 115.7–187 cm), the median weight was 59.46 ± 14.38 kg (range: 31–119.5 kg), the median BMI was 26.91 ± 3.42 kg/m² (range: 20.51–41.76 kg/m²), the median height Z-score was 1.07 ± 1.17 (range:–1.85 to 5.84), the median weight Z-score was 3.19 ± 0.95 (range: 0.77 to 6.2), and the median BMI-Z score was 2.98 ± 0.71 (range: 1.76 to 6.69), See Table 1.

Analysis of the gene spectrum for non-syndromic obesity

In this study, 32 patients with obesity (32/391,8.2%) were found to carry 18 non-syndromic obesity genes. The male-female ratio in the positive group was 2.2:1. The gene profiles of the positive group included UCP3, MC4R, PCSK1, NR0B2, NRP1, SEMA3B, DYRK1B, MRAP2, NRP2, NTRK2, PLXNA3, PLXNA4, PPARG, SEMA3C, SEMA3F, SEMA3G, SIM1, among which, UCP3 gene and MC4R gene were the most common, accounting for 19% (6/32) and 13%(4/32) respectively (Table 2).

UCP3 gene

6 cases carried mutations in the UCP3 gene, which is associated with severe obesity and type II diabetes (OMIM:601665), all located in the exon 3. One case was rated as likely pathogenic by ACMG and has been reported in the literature, while 5 cases were rated as variants of uncertain significance (VUS) but with a Bayesian score greater than 2 (Table 3).

MC4R gene

4 cases carried mutations in the MC4R gene, which is associated with obesity (BMI > 20) (OMIM:618406). 3 cases were rated as likely pathogenic by ACMG and have been reported in the literature, while one case was rated as VUS by ACMG with a Bayesian score of 3 (Table 3).

Table 1 General clinical data of 391 children and adolescents aged 7–14 years with obesity

N	Age at Visit (Year)	Ht(cm)	Wt*(kg)	BMI	Ht Z value	Wt Z value	BMI-Z value
Total(391)	10.35 ± 1.73	147.56 ± 11.13	59.46 ± 14.38	26.91 ± 3.42	1.07 ± 1.17	3.19 ± 0.95	2.98 ± 0.71
Male (301)	10.49 ± 1.65	148.20 ± 11.15	60.32 ± 14.36	27.08 ± 3.31	1.05 ± 1.17	3.32 ± 1.02	3.06 ± 0.74
Female (90)	9.88 ± 1.9	145.38 ± 10.82	56.55 ± 14.11	26.34 ± 3.7	1.12 ± 1.13	2.94 ± 0.74	2.71 ± 0.55

Abbreviations: Ht: Height; Wt: Weight; BMI: Body mass index

Table 2 Gene profile of nonsyndromic obesity in children and adolescents

No	Gene	Disease	OMIM	Inheritance	Case(*n* = 32)
1	UCP3	Severe obesity and type 2 diabetes	601,665	AD, AR, Mu	6(19%)
2	MC4R	Obesity(BMIQ20)	618,406	AD, AR	4(13%)
3	PCSK1	{Obesity, BMIQ12}	612,362		3(9%)
4	SEMA3D	?Obesity			3(9%)
5	NRP1	?Obesity(-; -)			2(6%)
6	SEMA3B	?Obesity(-;-)			2(6%)
7	NROB2	Obesity, mild, early-onset	601,665	AD, AR, Mu	2(6%)
8	DYRK1B	Abdominal obesity-metabolic syndrome 3	615,812	AD	1(3%)
9	MRAP2	{?Obesity, susceptibility to, BMIQ18}	615,457	AD	1(3%)
10	NRP2	?Obesity(-;-)			1(3%)
11	NTRK2	Obesity, hvperphagia, and developmental delay	613,886	AD	1(3%)
12	PLXNA3	?Obesity			1(3%)
13	PLXNA4	?Obesity			1(3%)
14	PPARG	Severe Obesity	601,665	AD, AR, Mu	1(3%)
15	SEMA3C	?Obesity			1(3%)
16	SEMA3F	?Obesity			1(3%)
17	SEMA3G	?Obesity			1(3%)
18	SIM1	?Obesity			1(3%)

Note:"?", before the phenotype name indicates that the relationship between the phenotype and gene is provisional. "{ }", indicate mutations that contribute to susceptibility to multifactorial disorders

Abbreviations: MC4R: melanocortin 4 receptor; UCP3:uncoupling protein 3;SEMA3B: semaphorin−3B; SEMA3D: semaphorin−3D; SEMA3F: semaphorin−3D; NR0B2: nuclear receptor subfamily 0,group b, member 2;NRP1:neuropilin 1;SIM1:SIM b hlh transcription factor 1;DYRK1B: dual-specificity tyrosine phosphorylation-regulated kinase 1B; SEMA3G: semaphorin−3G; PCSK1:proprotein convertase, subtilisin/kexin-type,1;MRAP2:melanocortin 2 receptor accessory protein 2;NTRK2:neurotrophic tyrosine kinase, receptor, type 2;PPARG: peroxisome proliferator-activated receptor-gamma

Other non-syndromic obesity genes

Among the 18 genes screened, PCSK1, SEMA3B, SEMA3C, SEMA3D, SEMA3F, SEMA3G, SIM1, NRP1, NRP2, PLXNA3, and PLXNA4 suggest a correlation with obesity, but currently, there is no information on their inheritance patterns and phenotypes. Considering the ACMG rating and Bayesian scores, these cases were included in the phenotype analysis to provide direction for future genetic etiology research of non-syndromic obesity (Table 3).

ACMG rating result analysis

Likely pathogenic cases rating by ACMG

Among the 18 non-syndromic obesity genes screened in this study, seven cases (7/391, 1.8%) were rated as likely pathogenic by ACMG, including three cases of the MC4R gene and one case each of SEMA3B, SEMA3D, SEMA3F, and UCP3 genes.

The MC4R gene has the clearest pathogenicity and is the most common, associated with obesity (BMI > 20) (OMIM:618406). Among the three MC4R cases, two carried the c.494G > A mutation, one of which was validated by family study to originate from a father with obesity and type 2 diabetes, suggesting that the MC4R gene may be a clear hotspot mutation gene for non-syndromic obesity in the Chinese population.

The mutation loci carried by the three cases with SEMA3B (case 94), SEMA3D (case 93), and SEMA3F (case 142) were all rated as likely pathogenic, pending further family analysis and functional experimental studies to assess their inheritance patterns and pathogenicity ratings.

VUS cases

Twenty-five cases (25/391, 6.4%) were rated as clinically uncertain by ACMG but had a Bayesian score above 2, including: UCP3 (5/25),PCSK1 (3/25),NRP1 (2/25),SEMA3D (2/25),DYRK1B (2/25),MC4R (1/25),MRAP2 (1/25),NRP2 (1/25),NR0B2 (1/25),NTRK2 (1/25),SEMA3G (1/25),PLXNA3 (1/25),PLXNA4 (1/25),PPARG (1/25),SEMA3B (1/25),SEMA3C (1/25),SEMA3G (1/25),SIM1 (1/25).

Among the non-syndromic obesity cases rated as clinically uncertain by ACMG, the UCP3 gene was the most common. Two cases had a Bayesian score of 5, for the NR0B2 and NRP1 genes, respectively, which may require further functional studies and could potentially serve as future genetic etiology sites for non-syndromic obesity (Table 3).

Table 3 Gene profile distribution in non-syndromic obese children

ID	Gene	Postion	Exon	DNA	AA	Mutation Type	ACMG	ACMG	*Score
146	MC4R	18q21.32	1	c.494G > A	p.R165Q	nonsynonymous	LP#	PM1;PM5;PP3;PS4	NA
394	MC4R	18q21.32	1	c.494G > A	p.R165Q	nonsynonymous	LP#	PM1;PM5;PP3;PS4	
187	MC4R	18q21.32	1	c.496G > A	p.V166I	nonsynonymous	LP#	PM1;BP4;PS4;PM2_Supporting	
266	UCP3	11q13.4	3	c.208 C > T	p.R70W	nonsynonymous	LP#	PS4;PM2_Supporting; PP3;PP4	
94	SEMA3B	3p21.31	5	c.169 C > T	p.Q57X	stopgain	LP	PVS1;PM2_Supporting	
93	SEMA3D	7q21.11	18	c.1992 C > G	p.Y664X	stopgain	LP	PVS1;PM2_Supporting	
142	SEMA3F	3p21.31	6	c.478 C > T	p.Q160X	stopgain	LP	PVS1;PM2_Supporting	
335	NR0B2	1p36.11	2	c.566G > A	p.G189E	nonsynonymous	VUS#	PM2_Supporting; PM3_Strong	5
224	NRP1	10p11.22	10	c.1646 C > G	p.P549R	nonsynonymous	VUS	PM2_Supporting; PP3_Strong	5
301	SIM1	6q16.3	3	c.213 C > G	p.S71R	nonsynonymous	VUS#	PS4;BP4_Moderate	3
61	DYRK1B	19q13.2	6	c.754 C > T	p.R252C	nonsynonymous	VUS	PM2_Supporting; PM5	3
167	MC4R	18q21.32	1	c.176T > C	p.L59S	nonsynonymous	VUS	PM1;PM2_Supporting	3
387	NRP2	2q33.3	17	c.2723 A > G	p.Y908C	nonsynonymous	VUS	PM2_Supporting; PP3_Moderate	3
353	SEMA3D	7q21.11	18	c.2260 C > T	p.Q754X	stopgain	VUS	PVS1_Moderate; PM2_Supporting	3
254	SEMA3G	3p21.1	7	c.809G > A	p.C270Y	nonsynonymous	VUS	PM2_Supporting; PP3_Moderate	3
228	UCP3	11q13.4	3	c.209G > A	p.R70Q	nonsynonymous	VUS	PM2_Supporting; PM5	3
258	UCP3	11q13.4	3	c.250G > A	p.G84S	nonsynonymous	VUS	PM2_Supporting; PP3_Moderate	3
166	UCP3	11q13.4	3	c.283 C > T	p.R95C	nonsynonymous	VUS	PM2_Supporting; PP3_Moderate	3
275	UCP3	11q13.4	3	c.601G > A	p.D201N	nonsynonymous	VUS	PM2_Supporting; PP3	2
341	UCP3	11q13.4	3	c.601G > A	p.D201N	nonsynonymous	VUS	PM2_Supporting; PP3	2
262	PCSK1	5q15	6	c.704T > C	p.V235A	nonsynonymous	VUS	PP3_Moderate	2
75	PCSK1	5q15	6	c.704T > C	p.V235A	nonsynonymous	VUS	PP3_Moderate	2
320	PCSK1	5q15	6	c.704T > C	p.V235A	nonsynonymous	VUS	PP3_Moderate	2
86	MRAP2	6q14.2	2	c.92G > A	p.G31E	nonsynonymous	VUS	PM5	2
124	NRP1	10p11.22	10	c.1654 C > T	p.R552W	nonsynonymous	VUS	PP3_Moderate	2
135	NTRK2	9q21.33	15	c.1635T > G	p.F545L	nonsynonymous	VUS	PM2_Supporting; PP2	2
195	SEMA3B	3p21.31	4	c.200T > C	p.L67P	nonsynonymous	VUS	PP3_Moderate	2
88	SEMA3C	7q21.11	12	c.1280 A > G	p.Y427C	nonsynonymous	VUS	PM2_Supporting; PP3	2
389	SEMA3D	7q21.11	18	c.1975G > T	p.D659Y	nonsynonymous	VUS	PP3_Moderate	2
383	PLXNA3	Xq28	19	c.3323T > C	p.V1108A	nonsynonymous	VUS	PM2_Supporting; PP3	2
19	PLXNA4	7q32.3	14	c.2752 A > G	p.M918V	nonsynonymous	VUS	PM2_Supporting; PP2	2
128	PPARG	3p25.2	7	c.1331 C > T	p.A444V	nonsynonymous	VUS	PM2_Supporting; PP3	2

Note: LP: ACMG rating as likely pathogenic; VUS: ACMG rating as variant of unknown significance;#: Reported in the literature; *Bayesian score: See reference 6 for criteria

Abbreviations: MC4R: melanocortin 4 receptor; UCP3:uncoupling protein 3;SEMA3B: semaphorin−3B; SEMA3D: semaphorin−3D; SEMA3F: semaphorin−3D; NR0B2: nuclear receptor subfamily 0,group b, member 2;NRP1:neuropilin 1;SIM1:SIM b hlh transcription factor 1;DYRK1B: dual-specificity tyrosine phosphorylation-regulated kinase 1B; SEMA3G: semaphorin−3G; PCSK1:proprotein convertase, subtilisin/kexin-type,1;MRAP2:melanocortin 2 receptor accessory protein 2;NTRK2:neurotrophic tyrosine kinase, receptor, type 2;PPARG: peroxisome proliferator-activated receptor-gamma

Correlation analysis of suspected pathogenic variation and clinical phenotype in 7 cases of non-syndromic obesity

After ACMG rating, seven cases were considered likely pathogenic, involving five genes: MC4R, SEMA3B, SEMA3D, SEMA3F, and UCP3. These seven patients included two males and five females, with the variation distribution being predominantly female. The age of onset of obesity was less than 10 years old, and they generally had a good appetite. The average age at the time of visit was 9.89 ± 1.96 years, the average weight was 54.2 ± 12.64 kg, the average height was 142.32 ± 12.85 cm, the average BMI was 26.34 ± 2.18, the average weight Z-score was 1.74 ± 1.72, the average height Z-score was 0.74 ± 0.87, and the average BMI-Z score was 2.84 ± 0.48.

Among the patients rated as likely pathogenic by ACMG: Five cases (all females) had advanced bone age (more than one year ahead of the actual age).Four cases (all females) had precocious puberty.Five cases had a family history of obesity, insulin resistance, hyperuricemia.Four cases had fatty liver, Four cases had acanthosis nigricans.Three cases had hypertriglyceridemia.Two cases had metabolic syndrome.Two cases had reduced glucose tolerance.One case had impaired liver function and a significant increase in urinary microalbumin (Table 4).

Table 4 Correlation analysis of suspected pathogenic variation and clinical phenotype in 7 cases of non-syndromic obesity

ID	146	392	187	142	94	93	266	Positive/*N*
Gene	MC4R	MC4R	MC4R	SEMA3F	SEMA3B	SEMA3D	UCP3	
Gender	male	female	female	male	female	female	female	Male: female 2:5
Age at Visit (year)	11.7	11.8	9.3	10.7	7.4	7.4	11.7	9.89 ± 1.96
BA	-	+	+	-	+	+	+	5/7
Wt(kg)	55	61.20	48.8	59.5	34.00	44.5	67.9	54.2 ± 12.64
Ht(cm)	148	153.10	139.7	154.6	120.50	130	153	142.32 ± 12.85
BMI	25.11	26.10	25.01	24.89	23.42	26.33	29.01	26.34 ± 2.18
Wt-Z Value	NA	NA	2.60	NA	2.15	3.53	NA	1.74 ± 1.72
Ht-Z Value	0.12	0.56	0.85	2.02	−0.45	1.22	0.57	0.74 ± 0.87
BMI-Z Value	2.38	2.28	2.66	2.61	2.91	3.65	2.72	2.84 ± 0.48
Acanthosis nigricans	+	-	+	+	-	+	+	5/7
Urinary microprotein(0–30)mg/L	-	-	-	-	-	-	276.38	1/7
ALT(5–45)U/L	-	-	-	-	-	-	171	1/7
AST(10–40)U/L	-	-	-	-	-	-	114	1/7
Uric acid(123–410)umol/L	457.7	546	438	-	-	-	555.6	4/7
FFA(0.4–0.9)mmol/L	-	-	-	-	-	-	1.04	1/7
Hypertriglyceridemia	+	+	-	-	-	-	+	3/7
Father BMI	26.03	29.4	25	23.66	23.50	26.2	24.74	26.06 ± 1.95
Mother BMI	20.81	22.62	22.32	18.36	30.00	22.12	23.78	23.54 ± 2.99
DM\obesity Family History	+	+	-	+	-	+	-	5/7
Ultrasound	+	+	-	+	-	-	+	4/7
OGTT	-	+	-	-	-	+	-	2/7
Insulin Secretion Test	-	+	+	-	-	+	+	5/7
Metabolic Syndrome	+	+	-	-	-	-	-	2/7
Precocious Puberty	-	+	+	NA	+	+	NA	4/5

Abbreviations: BA: Bone Age; Wt: weight; Ht: height; BMI: Body Mass Index; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; FFA: Free Fatty Acids; DM: Diabetes Mellitus; OGTT: Oral Glucose Tolerance Test

Comparison of clinical data of non-syndromic obesity gene positive group and negative group

In the general clinical data, there were 32 cases in the gene positive group and 391 cases in the negative group. Single factor analysis showed that Urinary microprotein, free T4(FrT4), serum alanine aminotransferase (ALT), serum glutamyl transpeptidyase (OGG), Uric acid, Serum phosphorus, paternal weight, family history of diabetes, obesity, hypertension. Impaired glucose tolerance (IGT), non-high-density lipoprotein cholesterol (non-HDL-C), and metabolic syndrome(MetS) showed significant differences, with statistical significance ($P < 0.05$), as shown in Tables 5 and 6.

In the regression analysis, genetic test outcomes were considered as the dependent variables, while indicators that exhibited statistically significant differences in univariate analysis were selected as independent variables for subsequent multivariate Logistic regression analysis. Specifically, urinary microprotein, fT4,ALT, GGT, uric acid, serum phosphorus, paternal weight, IGT, non-HDL-C and metabolic syndrome were chosen as independent variables. The analysis revealed that elevated blood phosphorus levels were significantly associated with the genetic predisposition to obesity, serving as an independent risk factor ($P < 0.05$).

Discussion

Obesity is the result of the combined effects of environmental and genetic factors. Traditionally, genetic obesity is divided into two major categories [6]: monogenic obesity and polygenic obesity. Although these forms are considered distinct, research on the mechanisms of both monogenic and polygenic obesity indicates [13, 14] that the central nervous system and neurons controlling "hedonic feeding" are the primary drivers in both types. The expression of mutations in monogenic obesity may be at least partially influenced by an individual's polygenic susceptibility to obesity [15].

Syndromic pediatric obesity is a rare condition [8], characterized by obesity as part of a unique set of clinical phenotypes, often including developmental delays and dysmorphic features. To date, approximately 25 different types of syndromic obesity have been reported [4, 16, 17], including Bardet-Biedl syndrome, Alström syndrome, Prader-Willi syndrome, and others.

Non-syndromic obesity refers to obesity that does not accompany other significant symptoms or diseases and is a more common type of obesity in children. Non-syndromic obesity can be further divided into monogenic obesity and polygenic obesity. Monogenic obesity is caused by mutations in a single gene, typically associated

Table 5 Comparison of clinical data of different groups with obesity

Group	Positive($n=32$)	Negative($n=359$)	Z/t Value	*P*
Age	10.50 ± 1.67	10.34 ± 1.74	0.258	0.612
BA	12.01 ± 1.69	11.44 ± 2.53	1.294	0.256
Wt	62.13 ± 14.96	59.25 ± 14.33	1.176	0.279
Ht	150.51 ± 11.67	147.33 ± 11.05	2.409	0.121
BMI	27.01 ± 3.21	26.90 ± 3.44	0.031	0.861
Wt-Z value	3.26 ± 0.84	3.19 ± 0.97	0.087	0.768
Ht-Z value	1.29 ± 0.90	1.76 ± 13.39	0.039	0.844
BMI-Z value	2.89 ± 0.62	2.99 ± 0.72	0.583	0.446
WC	86.47 ± 9.54	86.29 ± 10.07	0.009	0.924
HC	95.58 ± 8.31	92.62 ± 9.77	2.506	0.114
Urinary microprotein (mg/L)	22.03 ± 51.07	11.68 ± 17.77	5.88	0.016*
T(ng/dl)	38.83 ± 54.29	45.87 ± 69.46	0.281	0.596
IGF−1	277.77 ± 128.08	274.69 ± 142.90	0.011	0.918
IGF-BP3	6.25 ± 1.74	5.56 ± 1.78	3.469	0.063
ACTH	16.23 ± 17.03	13.04 ± 7.64	3.402	0.066
25-OH-VD	53.48 ± 12.72	59.79 ± 31.42	1.11	0.293
FT3	4.20 ± 0.70	4.30 ± 0.53	0.835	0.361
FT4	1.41 ± 0.63	1.28 ± 0.24	5.49	0.020*
TSH	2.88 ± 1.16	2.62 ± 1.38	0.919	0.338
ALT	55.72 ± 50.75	40.51 ± 37.32	4.184	0.042*
AST	39.62 ± 22.80	33.72 ± 18.38	2.653	0.104
ALP	278.66 ± 72.88	287.86 ± 167.01	0.087	0.769
GGT	35.28 ± 36.78	24.25 ± 19.50	7.179	0.008**
LDH	269.61 ± 57.82	262.03 ± 50.59	0.566	0.452
Uric acid	446.31 ± 117.47	409.92 ± 89.95	4.159	0.042*
FFA(0.4–0.9)	0.74 ± 0.30	0.70 ± 0.28	0.657	0.418
Serum phosphorus	1.72 ± 0.23	1.64 ± 0.20	4.501	0.035*
Father Ht(cm)	169.62 ± 5.12	172.25 ± 55.57	0.058	0.809
Father Wt(kg)	102.22 ± 145.01	76.47 ± 41.22	5.014	0.026*
Father BMI	25.42 ± 2.67	25.85 ± 4.34	0.238	0.626
Mother Ht(cm)	158.83 ± 4.94	158.10 ± 8.61	0.182	0.67
Mother Wt(kg)	60.90 ± 9.55	58.98 ± 9.84	0.881	0.349
Mother BMI	24.09 ± 3.77	23.47 ± 3.53	0.707	0.401
IGT	1.66 ± 0.48	1.82 ± 0.39	4.962	0.026*
HbA1c	5.14 ± 0.63	4.96 ± 0.56	3.009	0.084
HDL-C	1.78 ± 0.42	1.79 ± 0.41	0.015	0.902
non-HDL-C	1.75 ± 0.44	1.91 ± 0.29	7.941	0.005**

Note: * $P<0.05$ ** $P<0.01$

Abbreviations: BA: bone age; Wt: weight; Ht: Height; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; T:Testosterone; IGF−1:Insulin-like growth factor−1;IGF-BP3: insulin-like growth factor binding protein−3;ACTH: Adrenocorticotropic Hormone;25-OH-VD:25-Hydroxyvitamin D; FT3:free triiodothyronine; FT4:free thyroxine; TSH: thyroid stimulating hormone; ALT: alanine aminotransferase; AST: Aspartate Aminotransferase; alkaline phosphatase (ALP); GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; FFA: Free Fatty Acids; IGT: Impaired Glucose Tolerance; HbA1c: Glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol

with weight regulation, such as LEP (leptin), LEPR (leptin receptor), MC4R (melanocortin 4 receptor), and others. Most monogenic obesity mutations are found in cohorts of patients with severe and early-onset (< 10 years) obesity. Monogenic non-syndromic obesity is caused by pathogenic mutations in genes involved in leptin-melanocortin signaling, leading to extreme, early-onset obesity and hyperphagia.Eating disorders and obesity are commonly linked to mood disorders, such as depressive disorder [18].

Polygenic obesity results from the combined action of variations in multiple genes, each with a small effect, but cumulatively potentially leading to obesity. The inheritance pattern of this type of obesity is usually multifactorial, involving complex interactions between genetic and environmental factors. Polygenic obesity is the most common form of obesity and is more closely related to

Table 6 Comparison of clinical data of different groups

Item	Sort	Positive group	Negative group	χ2	*P*
Sex	Male	22(68.75)	279(77.72)	1.333	0.248
	Female	10(31.25)	80(22.28)		
Birt Weight	< 2.5 kg	1(3.33)	5(1.48)	0.606	0.739
	2.5–4kg	3(10.00)	37(10.95)		
	> 4 kg	26(86.67)	296(87.57)		
Family History	+	32(100.00)	217(60.45)	19.876	0.000**
	-	0(0.00)	142(39.55)		
IGT	+	11(34.38)	65(18.16)	4.925	0.026*
	-	21(65.63)	293(81.84)		
Hypertriglyceridemia	+	12(37.50)	86(24.02)	2.836	0.092
	-	20(62.50)	272(75.98)		
non-HDL-C	+	8(25.00)	33(9.19)	7.822	0.005**
	-	24(75.00)	326(90.81)		
Hypertension	+	9(28.13)	88(24.58)	0.197	0.657
	-	23(71.88)	270(75.42)		
Metabolic Syndrome	+	17(53.13)	98(27.30)	9.44	0.002**
	-	15(46.88)	261(72.70)		
Hyperfatty liver	+	17(54.84)	195(54.62)	0.001	0.981
	-	14(45.16)	162(45.38)		

Note: * $P < 0.05$ ** $P < 0.01$;Abbreviations: IGT: Impaired Glucose Tolerance

environmental factors, such as high-calorie diets and lack of exercise.

Over the past 20 years, with the rapid development of gene sequencing technology and in-depth research in obesity genetics, the boundary between monogenic and polygenic obesity has become increasingly blurred.

A total of 391 children with obesity, aged 7–14 years, were included in this study, with a male-to-female ratio of 3.35:1. The ratio of children carrying likely pathogenic mutations was 2:5, suggesting that girls with obesity are more likely to have genetic non-syndromic obesity and that genetic testing should be considered to rule out genetic non-syndromic obesity. Five girls with obesity all had advanced bone age, four were identified as having precocious puberty at an early age, and one case (case 266) was 11.7 years old at the time of visit, with the family unable to recall whether there was precocious puberty. Bone age testing indicated advanced bone age, suggesting that in clinical practice, obesity in children with precocious puberty may be one of the clinical clues.

This study found that the uncoupling protein 3 (UCP3) gene had the highest positive screening rate in children and adolescents with obesity, accounting for 19% (6/32). The UCP3 gene is located at 11q13.4 and includes 7 exons and 6 introns, primarily expressed in skeletal muscle and brown adipose tissue. The protein is involved in cellular fatty acid metabolism, and the UCP3 gene is associated with severe obesity and type 2 diabetes (OMIM:601665).

Uncoupling protein 3 (UCP3) is a protein-coding gene [19, 20], and research suggests that upregulation of UCP3 expression is associated with physical activity, fasting, and high-fat diets. When UCP3 activity is reduced, a decrease in energy expenditure is observed, while its increased expression is related to an increase in metabolic rate, thus helping to lower BMI. Current trends indicate that the association between UCP3 and obesity and diabetes is becoming increasingly evident. Polymorphism studies of UCP3 have found that rs15763, rs1800849, rs647126, rs7930460, rs1685356, rs1685354, rs11235972, and rs378190719 are associated with obesity.

This study found in children and adolescents with early-onset obesity that 6 cases carried 5 mutation sites of the UCP3 gene: c.208 C > T, c.209G > A, c.250G > A, c.283 C > T, c.601G > A (2 cases), which may be potential pathogenic sites for non-syndromic obesity. The mutations are all located in the third exon, suggesting that the third exon may be a hot spot for mutations. Among them, the UCP3 gene c.208 C > T has been previously reported [21, 22] and is associated with obesity and diabetes. This study found that the UCP3 gene c.208 C > T was heterozygously carried by a female with an age of onset less than 10 years, BMI of 29.01, and at the age of 11.7 at the time of visit, she already had symptoms such as liver function damage, hyperuricemia, advanced bone age, significantly increased urinary microalbumin, hypertriglyceridemia, and insulin resistance, suggesting that in clinical practice, early-onset severe adolescent obesity patients, if combined with symptoms such as liver function damage, are recommended to undergo genetic screening to rule out genetic non-syndromic obesity.

Melanocortin 4 receptor (MC4R) is a G protein-coupled receptor [23–26]that plays an important role in food intake, energy balance, and weight control. Autosomal dominant inheritance of MC4R variants causes early-onset obesity through increased appetite and decreased satiety. Wade et al. [27]conducted a functional characterization of non-synonymous variations in the MC4R gene in 5724 participants and found that the frequency of heterozygous loss-of-function (LoF) mutations in MC4R was 0.3% (1/337). This study suggests that genetic testing in patients with obesity may be important for adapting and creating new drug MC4R-treatment regimens in the future.The melanocortin 4 receptor (MC4R) plays a crucial role in regulating energy homeostasis and feeding behavior, which are closely linked to obesity. In addition to its metabolic functions, MC4R is also involved in immune regulation.

MC4R is a link between eating, immune response and brain functioning [28, 29].MC4R is expressed in various tissues, including the brain and peripheral immune cells, highlighting its broad involvement in both metabolic and immune pathways that contribute to the development of obesity and related comorbidities.

In this study of 391 non-syndromic patients with obesity, 4 cases carried MC4R gene mutations, and 3 cases

were rated as likely pathogenic by ACMG (previously reported in multiple studies), all located in the first exon. Two cases carried the c.494G > A mutation, suggesting that it may be a hot spot mutation in the Chinese population. All 4 children had a BMI greater than 25, indicating severe obesity, and all had a family history of obesity. All 4 had hypertriglyceridemia and presented with obesity phenotypes before the age of 6. This study found one case of MC4R gene c.176T > C mutation, which has not been previously reported and may be a potential pathogenic site, with further family analysis and functional validation studies to follow.

NR0B2 is a protein-encoding gene [30]. Diseases associated with NR0B2 include body mass index and quantitative trait loci. Its related pathways include androgen receptor signaling and estrogen receptor pathways. This study found one patient with a heterozygous mutation in the NR0B2 gene c.566G > A. Although ACMG rated it as VUS, there are already 2 obesity-related literature reports. One study based on a Japanese obese population found that carrying the NR0B2 gene c.566G > A and a luciferase reporter system indicated decreased expression after mutation [31]. Another study based on a Chinese adult obese population found carrying the NR0B2 gene c.566G > A heterozygous mutation but did not find family co-segregation [32]. This patient was a girl, 9 years and 9 months old at the time of visit, with a clinical phenotype of severe obesity with a BMI of 29, BMI-Z score of 3.25, insulin resistance, fatty liver, precocious puberty, etc., and a family history of obesity, suggesting that the NR0B2 gene c.566G > A may be associated with early-onset severe obesity in clinical practice.

DYRK1B is a protein-encoding gene. Diseases associated with DYRK1B include abdominal obesity metabolic syndrome 3 [33]. Its related pathways include neuroscience, apoptosis, and autophagy. GO annotations related to this gene include transferase activity, transfer of phosphorus-containing groups, and protein tyrosine kinase activity. DYRK1A is an important homolog of this gene. Abdominal obesity metabolic syndrome is characterized by abdominal obesity, high triglycerides, low levels of high-density lipoprotein cholesterol, high blood pressure, and high fasting blood sugar. Abdominal obesity metabolic syndrome3 is characterized by early-onset coronary artery disease, central obesity, high blood pressure, and diabetes. This study found one child with a DYRK1B gene variant, who had a family history of obesity, severe early-onset obesity, metabolic syndrome, and high blood pressure phenotype.

NRP1 is a protein-encoding gene [34] and diseases associated with NRP1 include hemangiopericytoma and neurofibroma. Its related pathways include the synovial cell apoptosis pathway and the p70S6K signaling pathway. NRP1 is a single-pass cell surface receptor that binds multiple ligands (such as semaphorins, vascular endothelial growth factor) and receptors (such as VEGFR2, integrins, plexins), affecting intracellular signaling, axon guidance, and the development of neuronal vasculature. Adipose tissue macrophages (ATMs) lacking the NRP1 gene have lower activity in lipid metabolism. This study found one obese child with NRP1 and NRP2 gene variants, which may provide insights for future non-syndromic obesity etiology diagnosis.

Hypothalamic melanocortin neurons play a key role in weight regulation, and the semaphorin 3 (SEMA3) signaling pathway may be related to obesity [35]. SEMA3-mediated signaling pathways drive hypothalamic melanocortin circuits involved in energy homeostasis. SEMA3G is an adipokine required for adipogenesis, adipogenesis, and insulin resistance, and is associated with obesity [36]. In genetic studies, 40 rare variations in SEMA3A-G and their receptors (PLXNA1–4; NRP1–2) were found in 573 individuals with severe obesity, and the variations disrupted secretion and/or signaling through various molecular mechanisms. Clinical studies show [37] that semaphorin 3 C is a novel adipokine involved in the pathophysiology of obesity and metabolism and is a biomarker representing the improvement of exercise-induced metabolically healthy obese young men. This study found three cases of SEMA3B, SEMA3D, and SEMA3F genes with likely pathogenic mutations, but further family analysis and functional studies are needed to clarify their pathogenicity.

This study found that among children and adolescents with non-syndromic obesity, the number of boys with obesity was significantly higher than that of girls. Thirty-two cases (32/391, 8.2%) carried 18 non-syndromic obesity genes, and 7 cases (7/391, 1.8%) were rated as likely pathogenic by ACMG. The UCP3 and MC4R genes were the most common genes for non-syndromic obesity and may be hot spot genes for non-syndromic obesity in China. ACMG rating and combined clinical symptom analysis showed that the gender distribution of obesity-related genes was more common in girls, suggesting that more attention should be paid to severe early-onset obesity in girls in clinical practice. Clinical phenotype and gene variation analysis suggested that children with non-syndromic obesity are prone to precocious puberty, insulin resistance, hypercholesterolemia, hyperuricemia, and other manifestations. Three cases of SEMA3B, SEMA3D, and SEMA3F genes with likely pathogenic mutations and insufficient mutation site rating, unclear inheritance patterns, and pending further family and functional studies to elucidate their pathogenic molecular mechanisms.

The genetics of obesity play a significant role in influencing clinical outcomes, and Parkinson's disease (PD) serves as an illustrative example of how genetic factors can impact therapeutic responses and disease

progression. Recent studies [29, 38, 39] have highlighted that genetic variability can affect the efficacy and safety of treatments, as well as the overall progression of diseases. For instance, in PD, genetic risk scores (GRS) derived from multiple genetic variants have been shown to influence the rate of disease progression and response to therapies. These genetic factors can also interact with environmental and lifestyle factors, further complicating the clinical picture. Understanding the genetic underpinnings of obesity and other complex diseases is crucial for developing personalized treatment strategies that can optimize clinical outcomes. By leveraging genetic information, clinicians can better predict disease trajectories, select appropriate therapies, and monitor treatment responses, ultimately leading to more effective and tailored medical interventions.As we enter the post-genomic era, it will be possible to use genetics to predict obesity for prevention and treatment in the future.

Conclusions

The findings of this study indicate that as the economic barriers to high-throughput sequencing diminish, there is potential for enhanced early diagnosis, which could revolutionize obesity management through timely intervention. This advancement may facilitate the identification of individuals with monogenic obesity who could significantly benefit from novel, personalized therapeutic strategies. Looking ahead, it is conceivable that we will be able to categorize the specific etiologies of obesity in individual patients, allowing for a more tailored approach to treatment. Embracing a personalized medicine paradigm could not only reverse the tide of the current obesity epidemic but also, more crucially, decrease the incidence of associated comorbidities, such as type 2 diabetes and cardiovascular diseases.

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Author contributions
HH: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing-review& editing.YY: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing-original draft.LYW, YL: Writing-review & editing.XLL: Investigation, Writing- review & editing. ZDG: Investigation, Writing- review & editing.

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Data availability
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. The datasets generated and/or analysed during the current study are available in the CNCB (China National Center for Bioinformation) repository, https://ngdc.cncb.ac.cn/gsa-human/s/rMSmJQOy.

Declarations

Ethics approval and consent to participate
The research protocol received ethical approval from [the Ethics Committee of the National Institute for Jiangxi Provincial Children's Hospital] Institutional Review Board (Approval No. JXSETYY-YXKY-20190003), and all study procedures rigorously compliance with to the ethical guidelines of the Helsinki Declaration (https://www.wma.net/policies-post/wma-declaration-of-helsinki/). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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