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Detecting monogenic obesity: a systematic exome-wide workup of over 500 individuals

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BACKGROUND/OBJECTIVES: Obesity poses a major public health concern. Although BMI heritability is estimated at 40–80%, genetic diagnostics remain challenging. This study aims to (i) assess the diagnostic yield of monogenic obesity in a large patient sample using exome-wide data, (ii) identify predictors to improve genetic testing criteria, and (iii) evaluate whether the identified genes are included in public obesity gene panels.

SUBJECTS/METHODS: We reviewed the genetic test results of 521 patients with obesity. 84.7% underwent whole-exome analysis, 15.3% were analyzed using a multi-thousand-gene panel.

RESULTS: Monogenic obesity was diagnosed in 5.8% of patients, while 7.1% carried a potentially obesogenic variant. Diagnostic yield was higher in children (6.3%) and patients with syndromic obesity (7.0%). Surprisingly, diagnostic yield was lower in severe obesity cases. 40% of patients with monogenic obesity carried variants in genes not included in current obesity panels.

CONCLUSION: Overall, 12.9% of patients had monogenic obesity or a potentially obesogenic variant. These findings suggest that genetic testing should not be limited to patients with extreme obesity. Current obesity panels miss crucial syndromic genes, demonstrating a need for more comprehensive panels and the superiority of whole-exome sequencing in obesity.

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INTRODUCTION

Obesity, defined as a body mass index (BMI) over 30 kg/m^2 in adults [1] and above the 97th percentile in children [2, 3], constitutes a profound and escalating global health challenge. Since 1990, obesity rates have more than doubled in adults and quadrupled in children, resulting in over one billion people worldwide living with obesity [4]. The etiology of obesity is complex, arising from a confluence of environmental, behavioral, and genetic determinants [5]. Among these, genetics is increasingly recognized for its critical role in influencing an individual's susceptibility to obesity [6, 7]. BMI heritability ranges from 40–50% in the general population and rises to 80% in subpopulations with obesity, underscoring a substantial genetic component in obesity risk [8–10].

Obesity of genetic origin is classified into a polygenic and a monogenic form, although recent findings indicate a significant overlap between these two groups [11]. Polygenic obesity arises from the cumulative impact of numerous genetic variants dispersed across various loci, with each variant showing only a minor association with the aggregate risk of obesity development [12]. Conversely, monogenic obesity is characterized by a condition in which a solitary genetic variant significantly elevates an individual's susceptibility to obesity, frequently resulting in severe obesity beginning at an early age [8]. Estimates on the prevalence of monogenic obesity vary, depending on each study's inclusion criteria and population. Considering only variants in known obesity genes classified as "pathogenic" and "likely pathogenic" according to the American College of Medical Genetics (ACMG) standards, diagnostic yields of 2.7% [13], 3.9% [14], to as high as 13% [15] have been reported in patients with obesity. This uncertainty emphasizes the need for additional research to provide a realistic insight into the genetic diagnostic yield of monogenic obesity.

Furthermore, monogenic obesity can be classified as either syndromic or non-syndromic, defined by the presence or absence of developmental delay, intellectual disability, and/or

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dysmorphisms (DD/ID/D). In recent years, pharmacological options targeting the underlying pathophysiological pathways have emerged. For example, setmelanotide, a melanocortin-4 receptor agonist, has shown efficacy in patients with impaired leptin-melanocortin signaling—a defect that may occur in patients with non-syndromic obesity (e.g., POMC deficiency) as well as in those with additional features (e.g., Bardet-Biedl syndrome) [16, 17]. However, as genetic diagnostics is expensive and not ubiquitously available, it is not part of routine screening for patients with obesity. Consequently, given that patients may benefit from a genetic diagnosis by receiving targeted treatment, there is a critical need for reliable predictors of genetic obesity to enhance diagnostic efficiency.

Most clinical research on monogenic obesity so far has focused solely on panels of selected obesity genes [13–15, 18–21]. By examining only a predefined set of genes in the analysis, variants can be missed, especially in genes where an obesity association has only recently been described. Although sequencing costs decline, making whole-exome sequencing (WES) increasingly accessible, reports of patients with obesity who largely received WES in a diagnostic setting, including evaluation of copy number variants, are currently missing. This gap poses a significant limitation in current studies related to monogenic obesity, highlighting the necessity for a broader investigative approach in this complex condition.

In this context, this exploratory study aims to (i) identify the diagnostic yield of monogenic obesity using exome-wide data in patients with syndromic and non-syndromic obesity. Additionally, it aims to (ii) determine traits predictive of a genetic diagnosis by phenotypically characterizing the cohort. Furthermore, this study aims to (iii) evaluate whether genes identified as associated with obesity in this cohort are also included in standard obesity gene panels.

METHODS

Patients

In order to identify patients with obesity who received WES or genetic diagnostics based on large clinical panels, we initially reviewed the results of individuals referred to the Institute of Human Genetics, University of Leipzig Medical Center, Germany, between 2018 and 2023 ($N = 16{,}840$). Patients were filtered by Human Phenotype Ontology terms assigned during presentation at our institute. In this study, we included 521 patients for whom obesity had been recorded. For the fourteen patients who underwent bariatric surgery, and their reported BMI at the time of testing did not align with established obesity definitions, pre-surgery BMI was considered. A flowchart describing the cohort selection process is presented in Supplementary Fig. 1.

Patient subgroups

Patients were divided into subgroups based on sex (male and female), age (adults and children, with children defined as those younger than 18 years at the time of testing), and the type of obesity (additional DD/ID/D or not). Furthermore, the severity of obesity was categorized: for adults, milder obesity was defined as a BMI of at least 30 but less than 40 kg/m², and severe obesity as a BMI of 40 kg/m² or higher. For children, milder obesity was classified as a BMI at or above the 97th and below the 99.5th percentile, and severe obesity as a BMI at or above the 99.5th percentile. Age- and sex-specific BMI percentiles for children were calculated using the German reference standards provided by Kromeyer-Hauschild et al. [2, 3].

Sequencing techniques

All individuals included in this cohort received next-generation sequencing (NGS)-based genetic diagnostics. The majority of probands, 84.5% ($n = 440$), received WES, using either a TWIST Human Core Exome kit ($n = 257$), TWIST Exome 2.0 ($n = 147$; TWIST Bioscience, San Francisco, USA), BGI Exome capture 59 M ($n = 26$; BGI, Shenzhen, China), Nextera Exome Rapid Capture v1.2 ($n = 7$; Illumina, San Diego, USA) or Agilent Exome SureSelect v6 ($n = 3$; Agilent, Santa Clara, USA). Sequencing was performed on Illumina NovaSeq 6000 (TWIST, TWIST 2.0), BGISEQ-500 (BGI), or an Illumina NextSeq- or HighSeq platform (Nextera, Agilent). The remaining 15.3% of patients ($n = 81$) received genetic diagnostics based on the TruSight One Sequencing Panel (4,813 genes, Supplementary Table 1), using the TruSight Rapid Capture Kit and Illumina NextSeq550. CNV analysis was carried out based on microarray or NGS data.

Variant interpretation

Evaluation of variants was performed using the software tools Varvis and Varfeed (Limbus, Rostock, Germany). All variants were classified in accordance with ACMG criteria [22], as well as the Association for Clinical Genetic Science (ACGS) Best Practice Guidelines [23]. Variants of unknown significance (VUS) were reevaluated in selected patients strongly suspected of having genetic obesity. Based on the variants reported to referring physicians and to the patients, subjects were categorized into three groups regarding a monogenic obesity diagnosis: "solved", "possibly solved", and "unsolved". The criteria for categorizing these groups were as follows: individuals with variants classified as "pathogenic" or "likely pathogenic" in genes with an established association with obesity, as documented by the Online Mendelian Inheritance in Man (OMIM) [24] and/or GeneReviews [25] databases, were considered "solved"; patients who had VUS reported in recognized obesity genes, and those with a (likely) pathogenic variant in a gene with limited, but some documented evidence for a monogenic obesity association, were classified as "possibly solved"; all other individuals were designated "unsolved".

Panel comparison

We investigated whether the obesity genes identified in this cohort were also included in publicly available obesity panels. To this end, we created one large panel consisting of all genes and loci listed in the obesity panels of two major sources for genetic panels, namely PanelApp Australia [26] and Genomics England PanelApp [27]. These genes were then compared with the genes affected in patients with monogenic obesity in our cohort. The combined public panel consisted of the following 57 loci: *ACBD6, ADCY3, AKR1C2, ALMS1, ARL6, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, C8orf37, CEP164, CEP19, CEP290, CPE, DYRK1B, GNAS, HTR2C, IFT172, IFT27, IFT74, INPP5E, KIDINS220, KSR2, LEP, LEPR, LZTFL1, MAGEL2, MC4R, MKKS, MKS1, MRAP2, MYT1L, NR0B2, NTRK2, PCSK1, PGM2L1, PHF6, PHIP, POMC, PPARG, SCAPER, SDCCAG8, SH2B1, SIM1, TRIM32, TTC8, TUB, VPS13B, WDPCP*, 15q11q13 recurrent region (PWS/AS, BP1-BP3, Class 1) Loss, 15q11q13 recurrent region (PWS/AS, BP2-BP3, Class 2) Loss, 16p11.2 recurrent region (includes *SH2B1*, distal region, BP2-BP3) Loss.

Statistical analysis

Permutation tests were performed using R Studio (version 2024.04.0, Build 735) with the R programming language (version 4.4.0). A significance level of 0.05 was used to determine statistical significance.

Use of large language models

ChatGPT (OpenAI, San Francisco, California, USA) was utilized to refine the clarity of writing in this manuscript. The model was employed selectively to enhance readability and coherence, without altering the substantive content or scientific rigor of the work.

RESULTS

Patient characteristics

This study included 521 individuals with obesity, comprising 76% children ($n = 396$) and 24% adults ($n = 125$). Slightly more than half of the patients were male (54.9%). 57.4% of the patients ($n = 299$) showed obesity with additional DD/ID/D, while the remaining 42.6% ($n = 222$) had obesity without these additional features. Regarding the severity of obesity, 25.5% of the individuals ($n = 133$) showed a milder form of obesity and 51.1% of the patients ($n = 266$) had severe obesity. For the remaining 23.4% ($n = 122$), no BMI data were recorded beyond the diagnosis of obesity. For detailed patient characteristics, see Supplementary Table 2.

Diagnostic yield

In this study, 5.8% of the patient cases ($n = 30$) were classified as solved and therefore received a monogenic obesity diagnosis. Among these individuals, eight had a (likely) pathogenic variant in

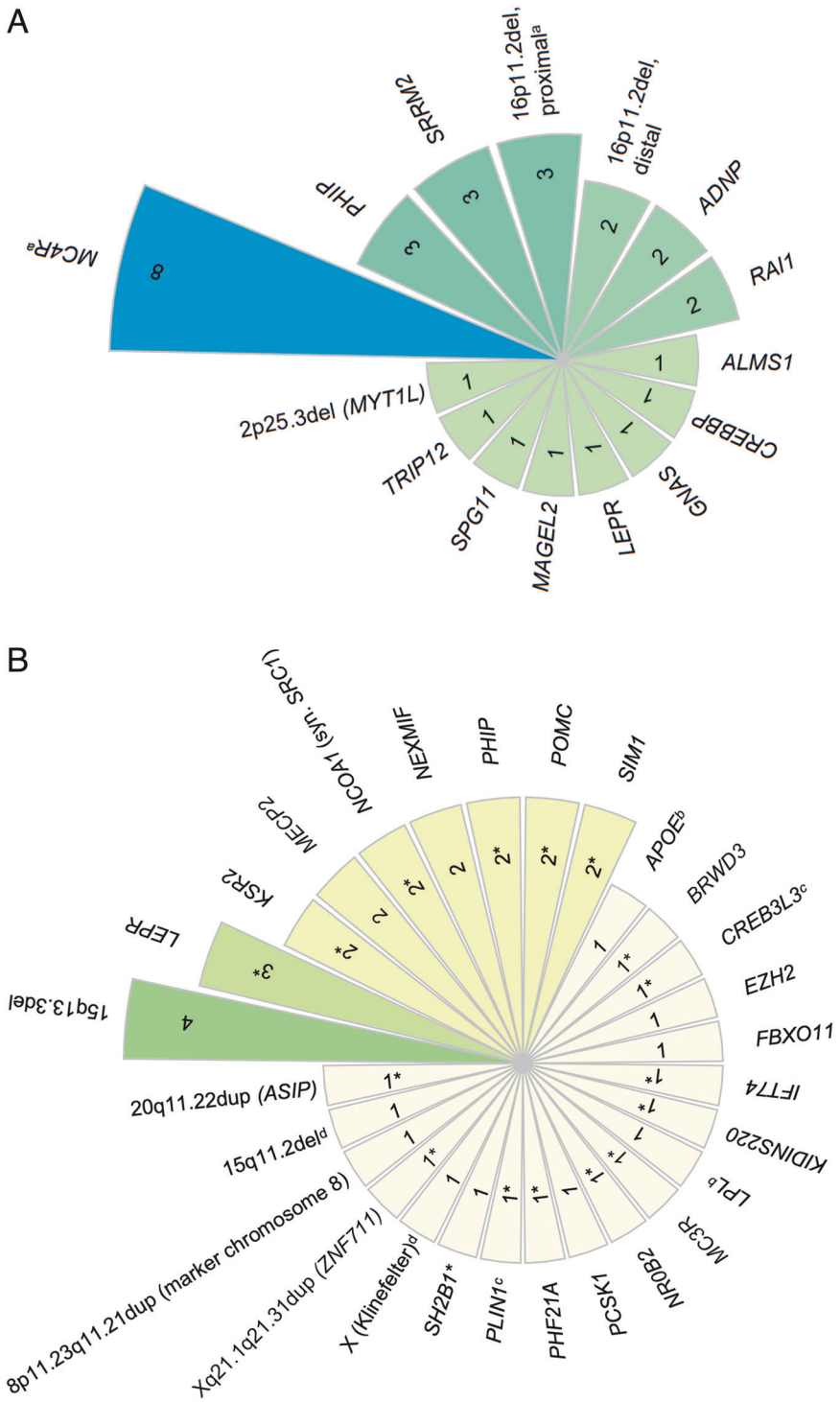

Fig. 1 Number of cases per locus. This radial plot shows how many individuals carry a (possibly) obesogenic variant for each locus. **A** Solved cases (a: patient with two affected loci). **B** Possibly solved cases (b, c, d: patients with two affected loci; *: patients with reported VUS in recognized obesity gene).

MC4R; five had a 16p11.2 microdeletion. Three patients had loss-of-function variants in *SRRM2*, and another three carried variants in *PHIP*. A complete list of affected genes is provided in Fig. 1A. Tables 1A and B present patient information and exact variant localization.

An additional 7.1% of patients ($n = 37$) were considered possibly solved regarding monogenic obesity, with a potentially obesogenic variant identified in these individuals. A list of impacted genes can be seen in Fig. 1B, and a list of patients and variants is available in Table 2A and B.

In total, 12.9% ($n = 67$) of the patients in this study carried a variant with a definite or suspected monogenic obesity association.

Predictive genetic obesity traits

Diagnostic yield was higher in children compared to adults, at 6.3% and 4.0%, respectively. Male and female patients exhibited similar

Table 1. Solved cases: patients and variants.

A. SNVs in solved cases

Patient[a]	Age group[b]	Sex	BMI (kg/m^2)	BMI percentile (children)	BMI SDS (children)	Gene	OMIM phenotype	Inheritance	Zygosity	Transcript	C-code	P-code	Classification	Additional DD/ID/D?
1	Child	M	19.8	97	1.91	*ADNP*	Helsmoortel-van der Aa syndrome (#615873)	AD	heterozygous	NM_015339.5	c.2156dup	p.(Tyr719*)	likely pathogenic	yes
2	Adult	M	30.2			*ADNP*	Helsmoortel-van der Aa syndrome (#615873)	AD	heterozygous	NM_001282531.3	c.1310dup	p.(Gly438Argfs*2)	likely pathogenic	yes
3	Child	F	24.4	100	3.78	*ALMS1*	Alstrom syndrome (#203800)	AR	compound heterozygous	NM_015120.4	c.8656C>T; c.11313_11316del	p.(Arg2886*); p.(Asp3771Glufs*20)	pathogenic	yes
4	Child	M	25.6	97.8	2.03	*CREBBP*	Rubinstein-Taybi syndrome 1 (#180849)	AD	heterozygous	NM_004380.3	c.4991G>T	p.(Arg1664Leu)	likely pathogenic	yes
5	Child	M	-	-	-	*GNAS*	Pseudohypoparathyroidism Ia (#103580)	AD	heterozygous	NM_000516.7	c.470_472del	p.(Glu157del)	likely pathogenic	yes
6	Child	M	57.9	100	4.23	*LEPR*	Obesity, morbid, due to leptin receptor deficiency (#614963)	AR	homozygous	NM_002303.6	c.133_136dup	p.(Tyr46*)	likely pathogenic	yes
7	Child	M	32.3	99.4	2.51	*MAGEL2*	Schaaf-Yang syndrome (#615547)	AD	heterozygous	NM_019066.5	c.1687C>T	p.(Gln563*)	likely pathogenic	yes
8	Child	M	48.3	100	3.44	*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.2	c.[105C>A110A>T]	p.[(Tyr35*,Asp37Val)]	pathogenic	no
9[c]	Adult	F	67.5			*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.3	c.380C>T	p.(Ser127Leu)	likely pathogenic	no
10	Child	F	25.8	99.9	3.16	*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.2	c.407C>T	p.(Ser136Phe)	pathogenic	no
11	Child	M	32.3	99.5	2.56	*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.2	c.466C>T	p.(Gln156*)	likely pathogenic	yes
12	Child	F	47	100	4.23	*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.2	c.542G>A	p.(Gly181Asp)	likely pathogenic	no
13	Child	M	22.6	98	2.04	*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.3	c.542G>A	p.(Gly181Asp)	likely pathogenic	no
14	Child	F	29.5	99.7	2.76	*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.2	c.542G>A	p.(Gly181Asp)	likely pathogenic	yes
15	Child	F	26.8	99.7	2.75	*MC4R*	Obesity (BMIQ20) (#618406)	AD	heterozygous	NM_005912.2	c.779C>A	p.(Pro260Gln)	likely pathogenic	no
16	Child	F	22.3	99.8	2.87	*PHIP*	Chung-Jansen syndrome (#617991)	AD	heterozygous	NM_017934.5	c.328C>T	p.(Arg110Cys)	likely pathogenic	yes
17	Child	F	37.5	99.9	3.15	*PHIP*	Chung-Jansen syndrome (#617991)	AD	heterozygous	NM_017934.6	c.3110C>A	p.(Ser1037*)	likely pathogenic	yes
18	Child	M	21.3	97.9	2.04	*PHIP*	Chung-Jansen syndrome (#617991)	AD	heterozygous	NM_017934.6	c.3947dup	p.(Tyr1316*)	likely pathogenic	yes
19	Child	M	-	-	-	*RAI1*	Smith-Magenis syndrome (#182290)	AD	heterozygous	NM_030665.3	c.859C>T	p.(Gln287*)	likely pathogenic	yes
20	Child	F	31.7	99.4	2.56	*RAI1*	Smith-Magenis syndrome (#182290)	AD	heterozygous	NM_030665.4	c.2396dup	p.(Gly800Trpfs*36)	pathogenic	yes
21	Adult	F	32			*SPG11*	Spastic paraplegia 11 (#604360)	AR	compound heterozygous	NM_025137.4	c.4790G>A; c.(5866+1_5867–1)_(6477+1_6478–1)del	p.(Trp1597*); p.(?), exon 31–34 deletion	pathogenic	yes
22	Adult	M	-			*SRRM2*	Intellectual developmental disorder, AD 72 (#620439)	AD	heterozygous	NM_016333.4	c.1585C>T	p.(Gln529*)	likely pathogenic	yes
23	Child	M	23.9	98.2	2.1	*SRRM2*	Intellectual developmental disorder, AD 72 (#620439)	AD	heterozygous	NM_016333.4	c.1585C>T	p.(Gln529*)	likely pathogenic	yes

Table 1. continued

A. SNVs in solved cases

Patient[a]	Age group[b]	Sex	BMI (kg/m^2)	BMI percentile (children)	BMI SDS (children)	Gene	OMIM phenotype	Inheritance	Zygosity	Transcript	C-code	P-code	Classification	Additional DD/ID/D?
24	Child	M	22.6	99.9	3.26	*SRRM2*	Intellectual developmental disorder, AD 72 (#620439)	AD	heterozygous	NM_016333.4	c.4583_4584del	p.(Val1528Glyfs*18)	pathogenic	no
25	Child	M	32	98.8	2.27	*TRIP12*	Intellectual developmental disorder, AD 49 (#617752)	AD	heterozygous	NM_001284214.1	c.4645del	p.(Ser1549Valfs*8)	likely pathogenic	yes

B. CNVs in solved cases

Patient[a]	Age group[b]	Sex	BMI (kg/m^2)	BMI percentile (children)	BMI SDS (children)	Locus	OMIM phenotype	CNV type	Zygosity	Genomic coordinates (hg38)	Classification	Additional DD/ID/D?
26	Child	F	35.1	100	5.25	2p25.3 (*MYT1L*)	Intellectual developmental disorder, AD 39 (#616521)	deletion	heterozygous	chr2:10501–2383145	pathogenic	yes
9[c]	Adult	F	67.5			16p11.2, proximal	Chromosome 16p11.2 deletion syndrome, 593 kbp (#611913)	deletion	heterozygous	chr16:29499949–30231685	pathogenic	no
27	Child	M	31.9	98.8	2.3	16p11.2, proximal	Chromosome 16p11.2 deletion syndrome, 593 kbp (#611913)	deletion	heterozygous	chr16:29790719–29805385 (Array recommended for exact location)	pathogenic	yes
28	Child	M	33.6	99.7	2.73	16p11.2, proximal	Chromosome 16p11.2 deletion syndrome, 593 kbp (#611913)	deletion	heterozygous	chr16:29951031–30583423	likely pathogenic	yes
29	Adult	F	34.5			16p11.2, distal	Chromosome 16p11.2 deletion syndrome, 220 kbp (#613444)	deletion	heterozygous	chr16:28773306–29219032	pathogenic	no
30	Child	F	31.7	99.5	2.57	16p11.2, distal	Chromosome 16p11.2 deletion syndrome, 220 kbp (#613444)	deletion	heterozygous	chr16:28823210–28990357	pathogenic	no

This table portrays detailed information on patients with monogenic obesity, including variant localization. **A** lists patients with SNVs, **B** shows those with CNVs.
AD autosomal dominant, *AR* autosomal recessive, *CNVs* copy number variants, *DD/ID/D* delevopmental delay/intellectual disability and/or dysmorphisms, *F* female, *M* Male, *SNVs* single nucleotide variants.
[a]Patients were numbered after the evaluation was completed; this had no impact on scientific integrity and anonymity.
[b]*Child* younger than 18 years at the time of testing, *adult* 18 years or older.
[c]Patient with variants in two loci.

Table 2. Possibly solved cases: patients and variants.

A. SNVs in possibly solved cases

Patient[a]	Age group[b]	Sex	BMI (kg/m^2)	BMI percentile (children)	BMI SDS (children)	Gene	OMIM phenotype	Inheritance	Zygosity	Transcript	C-code	P-code	Classification	Additional DD/ID/D?
31[c]	Adult	F	33.3			*APOE*	Hyperlipoproteinemia, type III (#617347)	-	homozygous	NM_000041.4	c.388T>C	p.(Cys130Arg)	risk factor	no
32	Child	M	21.4	98	2.06	*BRWD3*	Intellectual developmental disorder, X-L 93 (#300659)	XLR	hemizygous	NM_153252.5	c.4888dup	p.(Arg1630Lysfs*12)	VUS	yes
33[d]	Adult	M	33			*CREB3L3*	Hypertriglyceridemia 2 (#619324)	AD	heterozygous	NM_032607.2	c.733_738delinsGAAAAAT	p.(Lys245Glufs*130)	VUS	no
34	Child	M	30.3	99.3	2.44	*EZH2*	Weaver syndrome (#277590)	AD	heterozygous	NM_004456.4	c.472C>T	p.(His158Tyr)	likely pathogenic	yes
35	Child	F	31.6	99.5	2.54	*FBXO11*	Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities (#618089)	AD	heterozygous	NM_001190274.1	c.2084-93_2084-1del	p.?	likely pathogenic	yes
36	Child	F	20.4	99.5	2.54	*IFT74*	Bardet-Biedl syndrome 22 (#617119)	AR	compound heterozygous	NM_001099222.3	c.1623+1G>A; c.974+7A>G	p.?	VUS	yes
37	Adult	M	37.5			*KIDINS220*	Spastic paraplegia, intellectual disability, nystagmus, and obesity (#617296)	AD	heterozygous	NM_020738.4	c.2897C>T	p.(Ala966Val)	VUS	yes
38	Adult	M	64.1			*KSR2*	-	-	heterozygous	NM_173598.6	c.1847C>T	p.(Ser616Leu)	VUS	no
39	Adult	M	65.4			*KSR2*	-	-	heterozygous	NM_173598.6	c.2512C>T	p.(Arg838Cys)	VUS	no
40	Child	F	27.7	100	3.65	*LEPR*	Obesity, morbid, due to leptin receptor deficiency (#614963)	AR	compound heterozygous	NM_002303.5	c.1231_1233del; c.1990T>A	p.(Tyr411del); p.(Trp664Arg)	VUS	no
41	Child	F	23.2	100	3.73	*LEPR*	Obesity, morbid, due to leptin receptor deficiency (#614963)	AR	heterozygous	NM_002303.5	c.1835G>A	p.(Arg612His)	VUS	no
42	Child	M	21.9	99.5	2.55	*LEPR*	Obesity, morbid, due to leptin receptor deficiency (#614963)	AR	heterozygous	NM_002303.6	c.1967dup	p.(Glu657Glyfs*15)	likely pathogenic	no
31[c]	Adult	F	33.3			*LPL*	Combined hyperlipidemia, familial (#144250)	AD	heterozygous	NM_000237.3	c.914G>C	p.(Cys305Ser)	likely pathogenic	no
43	Child	M	29.1	99.7	2.78	*MC3R*	Obesity, severe, susceptibility to, BMIQ9 (#602025)	-	heterozygous	NM_019888.3	c.257T>C	p.(Leu86Pro)	VUS	no
44	Child	M	22.2	99.8	2.8	*MECP2*	Intellectual developmental disorder, X-linked syndromic 13 (#300055)	XLR	hemizygous	NM_001110792.2	c.455C>T	p.(Ala152Val)	pathogenic	yes
45	Child	F	37	100	3.71	*MECP2*	Rett syndrome (#312750)	XLD	heterozygous	NM_001110792.1	c.1200_1243del	p.(Pro401fs)	pathogenic	yes
46	Child	M	37.2	99.8	2.95	*NCOA1* (syn. *SRC1*)	-	-	heterozygous	NM_003743.4	c.3457C>T	p.(Gln1153*)	VUS	yes
47	Child	M	40.2	100	3.26	*NCOA1* (syn. *SRC1*)	-	-	heterozygous	NM_003743.4	c.3457C>T	p.(Gln1153*)	VUS	yes
48	Child	M	-	-	-	*NEXMIF*	Intellectual developmental disorder, X-linked 98 (#300912)	XLD	hemizygous	NM_001008537.3	c.67del	p.(Val23Serfs*13)	likely pathogenic	yes
49	Adult	F	-			*NEXMIF*	Intellectual developmental disorder, X-linked 98 (#300912)	XLD	heterozygous	NM_001008537.3	c.3310G>T	p.(Gly1104*)	likely pathogenic	yes
50	Child	F	35	98.5	2.2	*NR0B2*	Obesity, mild, early-onset (#601665)	AD, AR, Mu	heterozygous	NM_021969.3	c.712C>T	p.(Arg238Cys)	VUS	yes
51	Child	F	20.8	99.7	2.71	*PCSK1*	Obesity, susceptibility to, BMIQ12 (#612362)	-	heterozygous	NM_000439.4	c.1779del	p.(Thr594Profs*8)	likely pathogenic	no
52	Child	M	-	-	-	*PHF21A*	Intellectual developmental disorder with behavioral abnormalities and craniofacial dysmorphism with or without seizures (#618725)	AD	heterozygous	NM_001352027.1	c.885A>G	p.(Ile295Met)	VUS	yes
53	Child	M	-	-	-	*PHIP*	Chung-Jansen syndrome (#617991)	AD	heterozygous	NM_017934.7	c.214C>T	p.(Pro72Ser)	VUS	yes
54	Adult	M	31.9			*PHIP*	Chung-Jansen syndrome (#617991)	AD	heterozygous	NM_017934.7	c.1462G>T	p.(Asp488Tyr)	VUS	yes
33[d]	Adult	M	33			*PLIN1*	Lipodystrophy, familial partial, type 4 (#613877)	AD	heterozygous	NM_002666.4	c.224C>T	p.(Pro75Leu)	VUS	no
55	Child	M	48.5	100	3.49	*POMC*	Obesity, early-onset, susceptibility to (#601665)	AD, AR, Mu	heterozygous	NM_000939.4	c.73C>T	p.(Arg25Cys)	VUS	no
56	Child	M	46	100	3.42	*POMC*	Obesity, early-onset, susceptibility to (#601665)	AD, AR, Mu	heterozygous	NM_000939.4	c.706C>G	p.(Arg236Gly)	VUS	no
57	Child	M	25.4	100	3.53	*SH2B1*	-	-	heterozygous	NM_001387430.1	c.737_749del	p.(Met246Lysfs*4)	VUS	yes

Table 2. continued

A. SNVs in possibly solved cases

Patient[a]	Age group[b]	Sex	BMI (kg/m^2)	BMI percentile (children)	BMI SDS (children)	Gene	OMIM phenotype	Inheritance	Zygosity	Transcript	C-code	P-code	Classification	Additional DD/ID/D?
58	Child	M	25.7	99.9	3.21	*SIM1*	-	-	heterozygous	NM_005068.3	c.475T>C	p.(Ser159Pro)	VUS	yes
59	Child	F	29.3	99.8	2.91	*SIM1*	-	-	heterozygous	NM_005068.2	c.817G>A	p.(Asp273Asn)	VUS	no

B. CNVs in possibly solved cases

Patient[a]	Age group[b]	Sex	BMI (kg/m^2)	BMI percentile (children)	BMI SDS (children)	Locus	OMIM phenotype	CNV type	Zygosity	Genomic coordinates (hg38)	Classification	Additional DD/ID/D?
60[e]	Child	M	-	-	-	X-chromosome	Klinefelter syndrome			47, XXY		yes
61	Child	F	31.6	100	4.68	Xq21.1q21.31 (*ZNF711*)	Intellectual developmental disorder, XL 97 (#300803)	duplication	heterozygous	chrX:83887135–87060917	VUS	yes
62	Adult	M	-			8p11.23q11.21 (marker chromosome 8)	-	duplication	heterozygous	chr8:36905658–50017147	pathogenic	yes
60[e]	Child	M	-	-	-	15q11.2	Chromosome 15q11.2 deletion syndrome (#615656)	deletion	heterozygous	chr15:22626755–23039592	pathogenic	yes
63	Adult	M	34.9			15q13.3	Chromosome 15q13.3 microdeletion syndrome (#612001)	deletion	heterozygous	chr15:30079571–32222140	pathogenic	yes
64	Child	F	-	-	-	15q13.3	Chromosome 15q13.3 microdeletion syndrome (#612001)	deletion	heterozygous	chr15:30452995–32312810	pathogenic	yes
65	Child	F	34.5	99	2.3	15q13.3	Chromosome 15q13.3 microdeletion syndrome (#612001)	deletion	heterozygous	chr15:30605793–32149805	pathogenic	yes
66	Adult	M	31.2			15q13.3	Chromosome 15q13.3 microdeletion syndrome (#612001)	deletion	heterozygous	chr15:30651309–32222140	pathogenic	yes
67	Child	F	39.7	100	3.37	20q11.22 (*ASIP*)	-	duplication	heterozygous	chr20:34214053–34310533	VUS	no

This table portrays detailed information on patients with possible monogenic obesity, including variant localization. **A** lists patients with SNVs, **B** shows those with CNVs.
AD autosomal dominant, *AR* autosomal recessive, *CNVs* copy number variants, *DD/ID/D* delevopmental delay/intellectual disability and/or dysmorphisms, *F* female, *M* male, *Mu* multifactorial, *SNVs* single nucleotide variants, *VUS* variant of unknown significance, *XLD* X-linked dominant, *XLR* X-linked recessive.
[a]Patients were numbered after the evaluation was completed; this had no impact on scientific integrity and anonymity.
[b]*Child* younger than 18 years at the time of testing, *adult* 18 years or older.
[c,d,e]: Patient with variants in two loci.

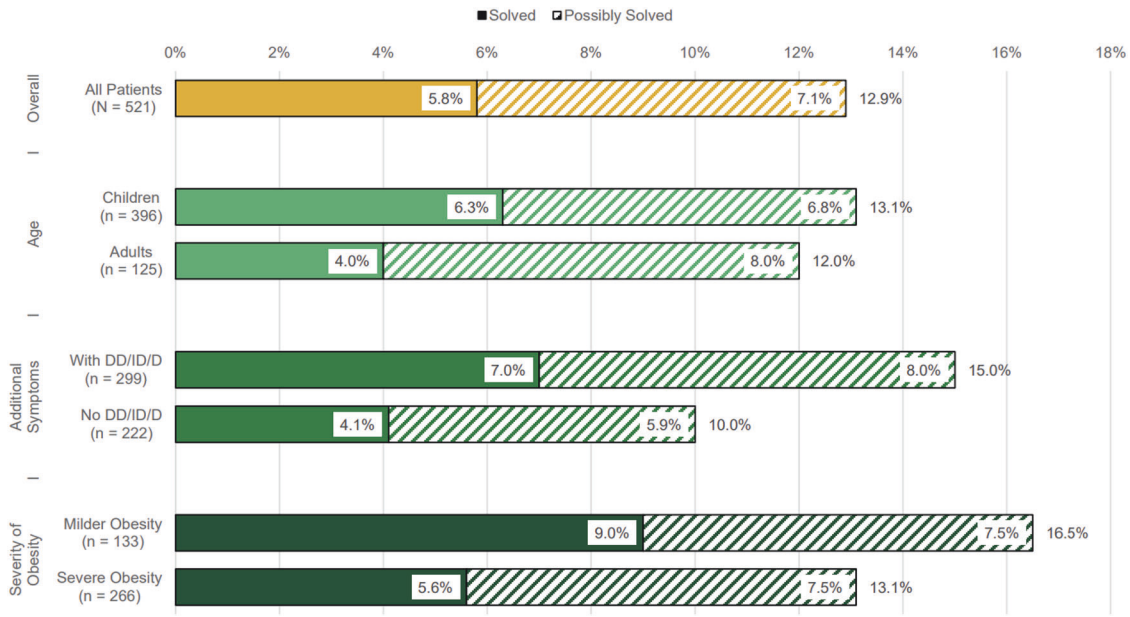

Fig. 2 Diagnostic yield in selected subgroups. This bar chart demonstrates the percentage of solved and possibly solved cases within several subgroups. Children, individuals with syndromic obesity, and patients with milder obesity showed higher genetic diagnostic yields. (DD/ID/D: developmental delay, intellectual disability, and/or dysmorphisms).

rates of monogenic obesity (5.9% vs. 5.5%). However, patients with obesity and additional DD/ID/D were more likely to have a monogenic obesity cause than those without these additional features (7.0% vs. 4.1%). This overall difference was driven exclusively by the pediatric subgroup; no difference was observed among adults. Notably, a higher BMI did not appear to increase the likelihood of a genetic obesity diagnosis. Among patients with severe obesity, 5.6% received a genetic obesity diagnosis, compared to 9% of individuals with milder obesity. A permutation analysis showed no significant statistical differences between groups for any of these results. An overview of diagnostic yields in selected subgroups can be found in Fig. 2, Supplementary Fig. 2 portrays further subgroup yields, while an extensive list of subgroup yields, including statistical results, is presented in Supplementary Table 3. Supplementary Table 4 lists genes affected in patients with and without additional syndromic features.

Comparison with obesity panels

Among all solved monogenic obesity cases from this study, only 60% (18/30) of the variants were in genes also listed in the combined obesity panel described above. This discrepancy primarily stems from missing genes associated with syndromic obesity. In patients without additional syndromic features, around 90% (8/9) of affected loci were included in the obesity panel. Conversely, in patients with additional DD/ID/D, only ~50% (10/21) of solved obesity cases could be explained solely by genes included in the obesity panel. Results are presented in Fig. 3A, B, a detailed overview can be found in Supplementary Table 4.

DISCUSSION

This large retrospective study analyzed the genetic test results of 521 patients with obesity who were referred to our institute for obesity or other diagnoses, most of whom underwent WES. Overall, 5.8% of patients ($n = 30$) received a monogenic obesity diagnosis, while a further 7.1% ($n = 37$) carried a possibly obesogenic variant. A higher diagnostic yield was found in children and individuals with additional DD/ID/D. Counterintuitively, people with severe obesity exhibited a lower diagnostic yield compared to those with milder obesity. Lastly, WES identified several genetic obesity causes that would have been missed by panel diagnostics.

The first aim of this study was to report the genetic diagnostic yield of obesity. With 5.8%, the diagnostic yield in this patient sample was comparable to that of other studies, with some reporting lower [14, 18] and others reporting higher results [15, 19]. Several systematic reviews support this outcome, estimating the prevalence of monogenic obesity at 5−10% in cohorts of patients with obesity [8, 28]. As the patients in this cohort primarily received broad WES instead of selected panel diagnostics, we had assumed that a higher number of genetic causes would be identified, which was, however, not the case. This lack of increase despite more extensive testing could potentially be explained by (i) the cohort selection process, (ii) the interpretation of variants in this study, and (iii) the underreporting of obesity as a comorbidity. Firstly, all patients with obesity who received genetic testing at the Institute of Human Genetics, Leipzig, were included in this analysis, regardless of primary indication. Therefore, in some cases, the initial diagnostic focus could have been elsewhere (e.g., epilepsy, DD), and clinical features prompting the clinician to order genetic testing did not necessarily need to suggest a genetic cause for the obesity as well (e.g., lack of early onset). Secondly, a distinction was made between patients with definitive and possible genetic obesity. Due to the strict criteria applied for genetic variant interpretation, it is possible that some variants classified as VUS may indeed have a profound obesogenic effect. As genetic variant evaluation improves with more available data, the classification of some variants may change in the future, including the possibly solved cases; the diagnostic yield in this cohort could potentially increase to 12.9% ($n = 67$). For variants with unclear implications, proof of loss of function should be sought by functional studies to guide treatment decisions, as exemplified by patients with variants in the leptin receptor (*LEPR*) [29]. A third factor that may alter the diagnostic yield in this study is incomplete documentation of obesity in the medical records of patients. Obesity was reported in less than 5% of all individuals in the in-house database we analyzed ($N = 16{,}840$, of which 12,291 were index patients comprehensively phenotyped). This percentage significantly differs from the obesity prevalence of ~19% in the German

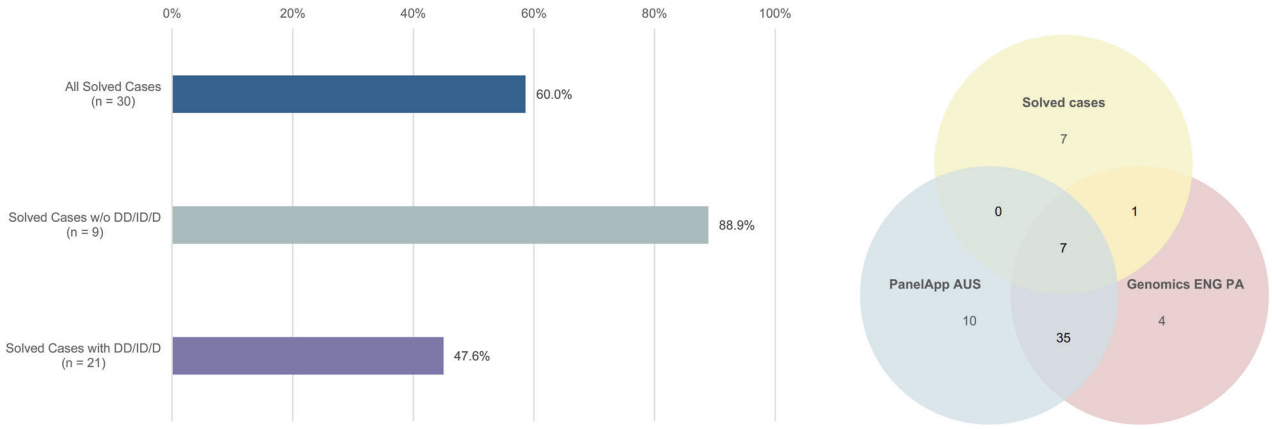

Fig. 3 Comparison of public obesity panel genes and genes affected in patients with monogenic obesity in this cohort. A shows the percentage of solved cases that could be identified using only obesity panels. It distinguishes between patients with non-syndromic and syndromic monogenic obesity. **B** shows a Venn diagram demonstrating the overlap between genes included in public obesity panels and genes affected in solved obesity cases in our cohort. (DD/ID/D developmental delay, intellectual disability and/or dysmorphisms, PA PanelApp, w/o without).

population [30]. While this discrepancy partly reflects the younger age distribution of our cohort, it also indicates underreporting of obesity when ordering genetic testing, especially if other, more severe symptoms are present. A recent study on the prevalence of comorbidities in individuals with neurodevelopmental delay found that clinical synopses on OMIM are missing about one-third of significantly enriched clinical features [31]. Although the authors did not explicitly mention obesity as one of those underreported comorbidities, the issue of obesity not having been documented when genetic testing was ordered was repeatedly encountered during this study. As the evaluation of genetic variants heavily relies on correct and comprehensive phenotyping [32, 33], this underscores the necessity to thoroughly report on obesity.

In our study of patients with monogenic obesity, *MC4R* emerged as the most commonly affected gene. Eight patients carried a relevant variant in this gene, representing 1.5% of the total cohort and 26.7% of those with monogenic obesity. This result is supported by the current literature, which has repeatedly shown *MC4R* to be the most frequent monogenic obesity cause [14, 15, 28, 34]. Additionally, five patients exhibited a 16p11.2 microdeletion, with three proximal and two distal deletions. Both forms are associated with obesity [35, 36], while recent research suggests higher obesity rates in patients with the 220 kbp distal deletion [37]. This is in part due to this region encompassing the gene *SH2B1*, which affects central leptin-melanocortin and insulin signaling pathways [38]. The third most frequently affected loci in patients with monogenic obesity in this cohort were *PHIP* and *SRRM2*, each impacted in three individuals. Variants in *PHIP* cause Chung-Jansen syndrome, linked to DD/ID/D and obesity [39–41]. This established gene-phenotype association enabled the reclassification of the variant of patient #16 (Table 1A) from VUS to likely pathogenic, confirming the diagnosis of Chung-Jansen syndrome. The initial assessment took place in 2016, when data on the effect of *PHIP* variants were still scarce. This demonstrates the ongoing process of genetic variant evaluation improving with new research, again highlighting that future interpretations of variants in this study may change. Lastly, loss-of-function variants in *SRRM2* have been described by Cuinat et al. in 2022 to cause a neurodevelopmental disorder with facial dysmorphisms that is associated with overweight/obesity. *SRRM2* encodes the SRm300 spliceosomal cofactor, and its haploinsufficiency may disrupt splicing of transcripts crucial for normal development and energy balance [42]. Interestingly, patient #24 (Table 1A) showed severe obesity with a BMI above the 99.9th percentile, but without DD/ID/D. This unusual phenotypic expression of *SRRM2* loss-of-function emphasizes the heterogeneity that can complicate the correct diagnosis of monogenic obesity. Adding to this, we excluded a girl with a pathogenic *SRRM2* variant because her BMI was just below the obesity threshold (96th percentile). This illustrates that while the clear distinction between overweight and obesity may benefit research standardization, it can also oversimplify what is essentially a continuum rather than a binary categorization.

Furthermore, in an additional 7.1% of patients ($n = 37$), possibly obesogenic variants were identified, warranting further research to investigate their relevance. Patient #51 (Table 2A) had a heterozygous, likely pathogenic variant in *PCSK1*, which encodes an enzyme critical to the central leptin-melanocortin pathway. While mono-allelic variants in *PCSK1* have been considered obesity-causing before [18, 14, 15, 43, 44], recent research questions the monogenic effect of heterozygous *PCSK1* variants on obesity [45], prompting us to assess these cases conservatively. Despite this, the truncating nature of the identified *PCSK1* variant suggests a potential loss of enzyme function, increasing the likelihood that it could cause obesity even in a heterozygous state [45, 46]. While haploinsufficiency is a likely mechanism of disease [44], a dominant negative effect may also be considered [45, 47], highlighting the relevance of functional variant analysis. Similarly, patients #55 and #56 (Table 2A) carried heterozygous variants in *POMC*. Recent studies suggest that these variants only slightly increase BMI, questioning their relevance in monogenic obesity [48]. Concurrently, an ongoing trial (EMANATE, RM-493-035) is investigating the effect of setmelanotide on patients with suspected genetic obesity who carry variants in genes involved in the *MC4R* pathway. For example, patients with heterozygous, likely pathogenic variants in *PCSK1* or *POMC* are eligible for inclusion. Additionally, we identified two patients (patients #46 and #47, Table 2A) with a variant in *NCOA1* [49]. Although this variant is classified as VUS, the patients fulfill the trial's inclusion criteria. While results from this trial are not yet published, this could potentially highlight a gap between genetic diagnostics and therapeutic consequences. Depending on the final data, the study might demonstrate that patients could receive targeted treatment even without a definitive genetic diagnosis. For now, the inclusion criteria already show that genetic test results enable these patients to participate in novel clinical trials—an important interim step toward more personalized obesity management.

The second aim of this study was to identify predictors for a genetic obesity diagnosis. Several characteristics indicated a

higher likelihood of a monogenic obesity diagnosis, though none of these changes were statistically significant. This aligns with the findings of Tamaroff et al., who also did not determine any significant predictive parameters [20]. However, other research indicates that features such as early onset of obesity (<5 years), hyperphagia [15], and consanguinity [50] can increase the likelihood of monogenic obesity and should inform clinical suspicion. The diagnostic yield was higher in children compared to adults, consistent with the report by Kleinendorst et al. [14]. Given the potential for personalized treatment [16, 17, 51] and psychological benefits, such as relief from self-blame [52], providing all children with obesity access to genetic testing could be beneficial. Nonetheless, pathogenic variants have also been identified in adults with obesity, which argues against excluding them from genetic testing, as highlighted by Tamaroff et al. [20]. One approach, alongside clinical suspicion, might be genetic testing before bariatric surgery [53]. The authors are aware that broader testing currently entails a high upfront cost. However, these costs are declining substantially and can offer downstream savings by guiding precision treatments, minimizing unsuccessful interventions, or informing decisions around bariatric surgery [54, 55]. In our study, 7.0% of patients with additional DD/ID/D ($n = 21$) received a genetic obesity diagnosis. This difference was driven by the pediatric subgroup, indicating that genetic obesity causes should be considered in children even when obesity is present only as an additional symptom. As the adult subgroups are relatively small (47 adults without DD/ID/D, Supplementary Table 3), larger studies are needed to investigate whether this finding extends to adult populations. Interestingly, the diagnostic yield was not increased in patients with severe obesity. In fact, patients with milder obesity received a genetic diagnosis more frequently. Similarly, Kleinendorst et al. [14, 15] and Tamaroff et al. [20] did not identify any significant BMI differences in individuals with and without relevant variants. This suggests that genetic testing should not be limited to cases of extreme obesity.

The third insight of this study is that large public obesity panels lack several obesity genes affected in this cohort, particularly in patients with additional DD/ID/D. Although PanelApp Australia explicitly includes genes associated with syndromic obesity [26], the evaluated panels only focus on severe early-onset obesity, thereby excluding genes associated with milder or later-onset phenotypes. As discussed, patient #24 (Table 1A) in this study carried a variant in *SRRM2*, which typically causes an intellectual developmental disorder and obesity [42]. However, the patient did not exhibit ID and would have been missed by obesity panel analysis alone. Likewise, Kleinendorst et al. identified six patients with a genetic obesity disorder typically associated with ID who did not have ID [15]. Variants in patients without fully penetrant phenotypes are at risk of escaping evaluation if panels do not consider the incomplete phenotypic expressivity of syndromic obesity.

In contrast, patient #6 (*LEPR*) and patients #11 and #14 (*MC4R*) carried pathogenic variants in genes typically associated with isolated obesity [56], but exhibited additional syndromic features (Table 1A). It is suspected that they harbor further pathogenic variants in DD-related genes, though none were identified in the analysis. This suggests that while individuals with syndromic obesity-associated variants can present with isolated obesity, the reverse is also possible. Consequently, extensive testing is needed to accurately diagnose these complex cases.

Moreover, ongoing research continues to expand the list of genes that determine body weight. For example, the rhodopsin-like G protein-coupled receptors (GPCRs) NPY2R and NPFFR2 [57], as well as the adhesion GPCR latrophilin 1 (ADGRL1/LPHN1) [58], significantly contribute to body weight regulation. Their relevance in causing obesity has been demonstrated at least in mice. Furthermore, loss-of-function variants in *BSN* and *APB1A* have demonstrated markedly larger effects on obesity risk than those observed for variants in *MC4R* [59]. A diagnostic approach using current panels might have missed such genes and their potential association with a human phenotype. This highlights the need for more comprehensive obesity panels and demonstrates the superiority of WES in obesity diagnostics.

Lastly, the dichotomic distinction between monogenic and polygenic forms of obesity remains a simplification. In this study, we classified monogenic obesity genes based on documented associations in the widely used databases OMIM and GeneReviews, which the clinical genetics community relies on for established gene-disease correlations. Nevertheless, the processes underlying body weight regulation are complex and influenced by multiple genetic and environmental factors. For example, loss-of-function variants in *MC4R* substantially raise obesity risk but can also be present in individuals without obesity [60]. This indicates that additional modifying factors can modulate penetrance, and labeling a case of obesity as strictly "monogenic" may not capture the full picture. Still, identifying such variants remains clinically meaningful, since a considerable number of individuals do present with severe or early-onset obesity primarily linked to a single-gene disruption, and these individuals may benefit from targeted interventions or specialized management.

Strengths and limitations

This study benefits from its large sample size of over 500 participants. Given the relatively low prevalence of monogenic obesity, this size allows for a more comprehensive analysis of the data and enhances the reliability of the findings. Moreover, patients in this cohort were not selected for diagnostics based on suspicion of genetically determined obesity. Thus, compared to other studies, the present cohort is less biased towards testing patients who strictly meet clinical criteria for monogenic obesity (such as hyperphagia or extreme BMI) and contributes to a broad and comprehensive perspective on the genetic causes of obesity. Most patients were analyzed using WES, which offers more extensive diagnostic capabilities compared to panel analyses. Variants were classified in accordance with ACMG and ACGS criteria, strengthening the significance and reproducibility of the results.

On the other hand, this study is limited by its retrospective approach. As discussed, obesity was likely not reported consistently, leading to several patients with obesity being missed by this analysis. Although population-level differences in genetic predisposition to obesity are recognized [61], the ethnic backgrounds of patients were not systematically recorded. This study was conducted using a clinical sample at a single institution, which may limit the generalizability of the findings to other populations and settings.

CONCLUSION

In this study of patients with obesity, 12.9% received either a definitive monogenic obesity diagnosis (5.8%) or carried a possibly obesogenic variant (7.1%). Although differences were not statistically significant, genetic diagnostic yield was higher in children and patients with additional DD/ID/D, suggesting a low threshold for genetic obesity testing in these groups. Diagnosis of genetic obesity did not correlate with higher BMI, suggesting that genetic testing should not be limited to cases of extreme obesity. Obesity panels would have missed 40% of patients with monogenic obesity in this cohort, primarily due to the incomplete inclusion of genes associated with syndromic obesity. Consequently, more comprehensive obesity panels are needed. To improve future diagnostic results, obesity should be reported consistently when ordering genetic testing. In conclusion, given that over one billion people globally are living with obesity, the possibility of a genetic origin should not be dismissed. Millions

may have a monogenic obesity cause and could potentially benefit from targeted treatment.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

RK conception and design of the study, data extraction, analysis, and interpretation, drafting and revision of the manuscript. DLD and AG: conception and design of the study, supervision of data collection and interpretation, drafting and revision of the manuscript, funding acquisition. HF, LB, MJ, AKi: conception of the study, data interpretation, drafting, and revision of the manuscript. MB, TS, RS, AKö, AKob, EW: patient coordination, interpretation of results, manuscript revision. RAJ, JL, DP: genetic diagnosis coordination, data analysis and interpretation, manuscript revision.

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COMPETING INTERESTS

MB received honoraria as a consultant and speaker from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Novartis, Novo Nordisk, Pfizer, and Sanofi. The other authors declare no competing financial interests.

ETHICAL APPROVAL

This study was approved and monitored by the Ethics Committee of the University of Leipzig, Germany (224/16-ek and 402/16-ek) and was conducted in concordance to the declaration of Helsinki. All families provided written informed consent for genetic testing. Institutional ethics approval was not required if testing was part of routine clinical care.

ADDITIONAL INFORMATION

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