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Syndromic and monogenic obesity in children from a population with frequent consanguinity: molecular spectrum and association with parental consanguinity

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Abstract

Purpose: Data on the molecular causes of childhood obesity in populations with frequent consanguinity are limited. We aimed to describe the molecular spectrum of syndromic and monogenic obesity in children from eastern Türkiye and to identify clinical features associated with a molecular finding.

Methods: We retrospectively reviewed 45 children from 41 families with obesity and at least one feature suggestive of genetic obesity who underwent stepwise genetic testing at a tertiary center between 2020 and 2026.

Results: A molecular finding was identified in 16 children (35.6%) from 12 families (29.3%): Bardet–Biedl syndrome (n = 6), *MC4R*-related obesity (n = 3), Alström syndrome (n = 2), *LEPR*-related obesity (n = 2), Prader–Willi syndrome (n = 1), Kleefstra syndrome (n = 1) and fragile X syndrome (n = 1). Thirteen children (81.3%) carried homozygous variants, including all three with *MC4R* variants. Four variants were previously unreported, and *BBS1* c.48-3C>G and *LEPR* c.1938G>T p.(Trp646Cys) were each found in two unrelated families. Parental consanguinity was more frequent in children with a molecular finding than in those without (85.7% vs. 32.1%; odds ratio 12.7, 95% confidence interval 2.3–68.9).

Conclusion: Genetic obesity in this cohort was predominantly autosomal recessive, with Bardet–Biedl syndrome as the leading diagnosis. Parental consanguinity, which was not a criterion for testing, was the feature most strongly associated with a molecular finding. In such populations, genetic testing should cover recessive ciliopathy and leptin–melanocortin pathway genes rather than *MC4R* alone.

What is Known:

- Monogenic and syndromic disorders cause severe early-onset obesity; heterozygous *MC4R* deficiency and Prader–Willi syndrome predominate in most series.

- Data from populations with frequent consanguinity are scarce.

What is New:

- In eastern Türkiye, Bardet–Biedl syndrome was the leading diagnosis, 81% of findings were homozygous and four variants were previously unreported.
- Parental consanguinity, not a testing criterion, was most strongly associated with a molecular finding.

Keywords: Pediatric obesity; Monogenic obesity; Syndromic obesity; Bardet–Biedl syndrome; Consanguinity; Genetic testing

Abbreviations: ACMG, American College of Medical Genetics and Genomics; BMI, body mass index; CES, clinical exome sequencing; CI, confidence interval; CMA, chromosomal microarray analysis; HOMA-IR, homeostasis model assessment of insulin resistance; MLPA, multiplex ligation-dependent probe amplification; OR, odds ratio; SDS, standard deviation score; VUS, variant of uncertain significance; WES, whole-exome sequencing

Introduction

Childhood obesity usually reflects polygenic susceptibility and environmental factors, but rare monogenic and syndromic disorders cause severe early-onset obesity [1–4]. Monogenic forms mostly involve the leptin–melanocortin pathway, whereas syndromic forms combine obesity with neurodevelopmental, renal, ocular, endocrine or skeletal manifestations [5, 6]. A molecular diagnosis guides surveillance and genetic counseling and, for some disorders, opens access to targeted treatment [7–10].

Guidelines recommend considering genetic testing in children with severe early-onset obesity, particularly when accompanied by hyperphagia, a family history of extreme obesity, developmental delay or dysmorphic features [11, 12]. Reported diagnostic yields range from 3.1% in a Belgian real-world cohort [13] and 5.8% in an exome-wide workup of 521 children and adults [14] to 10.4% in a Turkish multicenter study of non-syndromic early-onset obesity [15], reflecting differences in patient selection, testing strategy and the definition of a positive result [16].

In most series, heterozygous *MC4R* deficiency and Prader–Willi syndrome are the leading diagnoses [6, 17]. Where consanguineous marriage is common, as in Türkiye [18], autosomal recessive disorders are expected to be over-represented, yet data from such populations remain limited [15, 19], and whether parental consanguinity helps to identify the children most likely to receive a molecular diagnosis is uncertain.

We therefore describe the molecular spectrum of syndromic and monogenic obesity in children evaluated at a tertiary center in eastern Türkiye, report the yield of a stepwise testing strategy per child and per family, and explore which features, including parental consanguinity, were associated with a molecular finding.

Materials and methods

Study design and participants

This retrospective cohort study was conducted at the Pediatric Endocrinology Clinic of Van Training and Research Hospital, a tertiary referral center in eastern Türkiye, and is reported in accordance with the STROBE statement [20]. Children with obesity, defined as a body mass index (BMI) standard deviation score (SDS) ≥ 2.0 according to Turkish references [21], who underwent genetic evaluation between November 2020 and January 2026 were eligible. Genetic evaluation was requested when at least one of the following features was present: obesity onset at or before 5 years of age, hyperphagia, developmental delay or intellectual disability, dysmorphic features or congenital anomalies, or obesity in at least one biological parent [11, 12]. Of 46 children tested, one met none of these features on record review and was excluded; the cohort therefore comprised 45 children from 41 families, including four sibling pairs (Fig. 1).

Clinical definitions and assessment

Clinical variables were extracted from the medical records. Age at obesity onset was based on caregiver report and earlier growth records. Hyperphagia was recorded when caregivers consistently reported excessive food seeking, persistent hunger despite recent meals, or marked distress when food was restricted; no validated questionnaire was used. Developmental delay or intellectual disability was based on developmental history, school performance and the need for special education. Dysmorphic features were assessed by pediatric endocrinologists and clinical geneticists. Night eating was defined as recurrent eating after falling asleep. Parental consanguinity and its degree were recorded from the family history; any reported parental relatedness was coded as consanguinity. Height and weight were measured with a Harpenden stadiometer and a calibrated digital scale, and SDS were calculated using Turkish references [21]. Fasting plasma glucose, insulin, glycated hemoglobin (HbA1c), alanine aminotransferase (ALT), lipids, thyroid-

stimulating hormone (TSH) and free thyroxine were measured with standardized automated methods, and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin ($\mu\text{IU/mL}$) $\times$ fasting glucose (mg/dL)/405. Unless stated otherwise, data refer to the first evaluation.

Genetic testing

Testing followed the stepwise approach used at our institution (Fig. 1). Conventional karyotyping was the first-tier test. When the phenotype pointed to a specific disorder, a targeted test followed: multiplex ligation-dependent probe amplification (MLPA) of 15q11.2–q13 for suspected Prader–Willi syndrome, *FMRI* CGG-repeat analysis, chromosomal microarray analysis (CMA), single-gene sequencing (e.g., *MC4R*, *ALMS1*, *GNAS*) or a Bardet–Biedl syndrome gene panel. Children without a diagnosis proceeded to clinical exome sequencing (CES), and whole-exome sequencing (WES) was performed when CES was non-diagnostic and suspicion persisted. Affected siblings of a diagnosed child were tested for the familial variant or gene. Testing stopped once a diagnosis was established. Segregation was studied in available parents, and all analyses were performed in accredited diagnostic laboratories.

Variant interpretation and definition of a molecular finding

Sequence variants were classified according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) criteria [22], copy-number variants according to the ACMG/ClinGen standards [23], and variants are described according to Human Genome Variation Society nomenclature [24]. A variant was considered previously unreported when absent from ClinVar [25], the Genome Aggregation Database [26] and the published literature (PubMed; last accessed 24 August 2026).

A molecular finding was defined as a pathogenic or likely pathogenic sequence variant, a pathogenic copy-number variant or a full-mutation repeat expansion consistent with the phenotype. After multidisciplinary review, a homozygous *LEPR* variant of uncertain significance (VUS) found in two children with a concordant phenotype was also counted; it was not reclassified, and yields are reported with and without it. Findings were grouped as syndromic obesity (Bardet–Biedl, Alström and Prader–Willi syndromes), monogenic non-syndromic obesity (*MC4R* and *LEPR*), together termed genetic obesity, and other genetic diagnoses in which obesity occurs but is not a defining feature (Kleefstra and fragile X syndromes) [2, 5, 27, 28].

Statistical analysis

Analyses were performed with Python 3.13 (SciPy 1.18.1 and statsmodels 0.15.0). Continuous variables are presented as mean $\pm$ SD and compared with Welch’s t test when approximately normally distributed (Shapiro–Wilk test), and otherwise as median (interquartile range, IQR) and compared with the Mann–Whitney U test. Categorical variables were compared with the χ^2 test, or Fisher’s exact test when an expected count was below 5. Available data were used without imputation. Laboratory comparisons were exploratory and not adjusted for multiple testing. Diagnostic yield was calculated with exact (Clopper–Pearson) 95% confidence intervals (CIs) per child and per family. Associations with a molecular finding were examined with logistic regression. Given the small number of events, multivariable analysis was limited to two prespecified models: model 1 included age at obesity onset and dysmorphic features, and model 2 added parental consanguinity. Sensitivity analyses retained one child per family, were restricted to genetic obesity, or excluded the two children with the *LEPR* VUS. The regression analyses were exploratory. Two-sided p values <0.05 were considered significant.

Use of large language models

Large language models (ChatGPT, OpenAI; Claude, Anthropic) were used to assist with language editing, restructuring of the manuscript and statistical analysis code. They are not authors. All analyses were verified against the source data, and the authors take full responsibility for the content.

Results

Study cohort and diagnostic yield

The 45 children (23 boys, 51.1%; 41 families) had a mean age at first evaluation of 7.1 ± 4.0 years (range 0.5–15.5), a median age at obesity onset of 4.0 years (IQR 1.0–5.0) and a median BMI SDS of 3.40 (IQR 2.95–3.94). Obesity had begun at or before 5 years in 35 of 44 children with available data (79.5%); hyperphagia, developmental delay, dysmorphic features and parental obesity were present in 34 (75.6%), 20 (44.4%), 16 (35.6%) and 15 (33.3%), respectively. Parents were related in 21 of 42 children with available data (50.0%) and in 17 of 38 families (44.7%) (Table 1).

A molecular finding was identified in 16 of 45 children (35.6%; 95% CI 21.9–51.2) from 12 of 41 families (29.3%; 95% CI 16.1–45.5) (Fig. 1). Fourteen children (31.1%; 95% CI 18.2–46.6) had genetic obesity. Without the two children with the *LEPR* VUS, 14 children (31.1%) had a pathogenic or likely pathogenic finding; applying both restrictions left 12 (26.7%; 95% CI 14.6–41.9). Diagnoses were established by CES in six children, single-gene sequencing in four, familial variant testing in two, a Bardet–Biedl syndrome panel, WES, CMA and *FMRI* analysis in one each (Table 2). Of the 29 children without a finding, 20 (69.0%) had completed exome sequencing; nine had cytogenetic and/or targeted testing only.

Molecular spectrum

Bardet–Biedl syndrome was the most frequent diagnosis (six children from four families) and was genetically heterogeneous (*BBS1*, *TTC8* and *ARL6*, two children each), followed by *MC4R*-related obesity (n = 3), Alström syndrome (n = 2), *LEPR*-related obesity (n = 2), Prader–Willi syndrome (n = 1), Kleeftstra syndrome (n = 1) and fragile X syndrome (n = 1) (Table 2). Prader–Willi syndrome was diagnosed in a boy with neonatal hypotonia, feeding difficulties, cryptorchidism, hyperphagia and intellectual disability, in whom CMA identified a 6.1-Mb 15q11.2–q13.1 deletion that was confirmed by MLPA.

Thirteen of the 16 children (81.3%) carried homozygous variants: all six with Bardet–Biedl syndrome, both with Alström syndrome, both with the *LEPR* variant and all three with *MC4R* variants (two siblings with p.(Asp126Glu) and an unrelated child with c.232_233insGAA). Parents were related in 11 of the 12 homozygous children with available information. *BBS1* c.48-3C>G was homozygous in two unrelated boys (P2 and P7), one without reported parental consanguinity, and *LEPR* c.1938G>T p.(Trp646Cys) in two unrelated girls with extreme early-onset obesity (P11 and P12; BMI SDS 8.54 and 6.43), whose parents in one family were heterozygous carriers. Four variants were previously unreported: *TTC8* c.1214T>A p.(Leu405Ter), *ARL6* c.184A>T p.(Ser62Cys), *MC4R* c.232_233insGAA p.(Pro78delinsArgThr) and *EHMT1* c.981+1G>C.

Features associated with a molecular finding

Children with a molecular finding were younger at first evaluation (5.2 ± 3.7 vs. 8.2 ± 3.9 years; $p = 0.015$), had earlier obesity onset (median 1.0 vs. 4.0 years; $p = 0.023$) and more often had dysmorphic features (56.3% vs. 24.1%; $p = 0.031$) (Table 1). Developmental delay (62.5% vs. 34.5%; $p = 0.070$) and hyperphagia (93.8% vs. 65.5%; $p = 0.067$) were more frequent, but not significantly so; sex, BMI SDS, parental obesity and pubertal status did not differ. Triglycerides and HbA1c were higher in children with a finding; given the age difference, these unadjusted comparisons were not interpreted further.

The largest difference concerned parental consanguinity: 12 of 14 children with a molecular finding (85.7%) vs. 9 of 28 without (32.1%; $p = 0.001$; OR 12.7, 95% CI 2.3–68.9) (Table 3). In model 1, earlier onset (adjusted OR 0.62 per 1-year increase in age at onset; 95% CI 0.42–0.91) and dysmorphic features (adjusted OR 8.41; 95% CI 1.58–44.83) were associated with a finding. In model 2, consanguinity remained associated (adjusted OR 6.64; 95% CI 1.05–41.80), whereas the estimates for onset and dysmorphic features were attenuated and their CIs included 1. The association persisted with one child per family (8 of 10 vs. 9 of 28 families; OR 8.4, 95% CI 1.5–48.1; Fisher’s exact $p = 0.023$) and when restricted to genetic obesity or excluding the *LEPR* VUS (11 of 13 children; OR 11.6, 95% CI 2.1–63.7; $p = 0.003$). The two children with a finding and unrelated parents had Prader–Willi syndrome (P1) and Bardet–Biedl syndrome due to the recurrent *BBS1* variant (P2).

Discussion

In this cohort from eastern Türkiye, about one-third of children selected for genetic evaluation, and 29% of families, had a molecular finding. The spectrum was predominantly autosomal recessive, with Bardet–Biedl syndrome as the leading diagnosis and homozygous variants in 13 of 16 children. Parental consanguinity was the feature most strongly associated with a molecular finding, two variants recurred in unrelated families, and four variants had not been reported before.

Our yield exceeds that of a Belgian cohort tested with a 44-gene panel [13], an exome-wide workup of 521 individuals [14] and a Turkish multicenter study that screened 41 genes in 105 children with non-syndromic early-onset obesity [15]. Our cohort included syndromic phenotypes and siblings, and testing extended to cytogenetic, copy-number, repeat-expansion and exome analysis. We therefore report yields per family and under restrictive definitions; even under the strictest, about one in four children had a diagnosis.

The distribution of diagnoses differed from most series, in which heterozygous *MC4R* deficiency and Prader–Willi syndrome predominate [6, 17]. Bardet–Biedl syndrome accounted for four of 12 diagnosed families, and all three children with *MC4R* variants, born to first-cousin parents, were homozygous. A strategy limited to *MC4R* sequencing would have identified three of the 16 children. In populations with frequent consanguinity, testing should cover recessive ciliopathy and leptin–melanocortin pathway genes, and exome sequencing after a negative targeted test appears justified. The spectrum reflects a phenotype-selected referral population, not population prevalence.

Early-onset obesity and syndromic features are established indications for testing [11, 12] and were associated with a molecular finding in our data. However, both were also reasons for testing and define several syndromes, which may inflate their apparent effect. Parental consanguinity differs: it was neither a testing criterion nor part of any diagnostic definition, and its association persisted at the family level, in genetic obesity alone and after adjustment for onset and dysmorphic features. Previous attempts to identify predictors have been inconsistent; no clinical feature improved the yield in the Belgian cohort [13], whereas an Italian study proposed a score based on age at onset, family history and a hyperphagia questionnaire [29]. Where consanguineous marriage is common [18], asking about parental relatedness is a simple addition to the assessment of a child with severe obesity. The estimate was imprecise, however, and two children with a finding had unrelated parents, so the absence of consanguinity should not be used to withhold testing from children who meet guideline criteria.

Hyperphagia was reported in 94% of children with a finding but also in two-thirds of those without; without a validated instrument, caregiver-reported hyperphagia has limited specificity [30, 31]. Parental obesity was uninformative, as expected when most diagnoses are recessive.

259 *BBS1* c.48-3C>G, first reported in a Turkish child with Bardet–Biedl syndrome [32], was
260 homozygous in two unrelated boys in our cohort, one of whom had unrelated parents; its
261 occurrence in three unrelated families suggests that this allele may be relatively frequent in
262 Türkiye. *LEPR* p.(Trp646Cys) was previously reported in a girl with severe early-onset
263 obesity who was also homozygous for p.Pro316Thr, which limited attribution of her
264 phenotype [33]; structural modeling suggests that p.Trp646Cys disrupts the fibronectin type
265 III domain interface required for signaling [34]. Two further unrelated homozygous children
266 without p.Pro316Thr, with a concordant phenotype, no alternative diagnosis and segregation
267 in one family, add evidence relevant to its classification. The variant nevertheless remains a
268 VUS, because leptin concentrations and functional studies were not available, and haplotype
269 analysis would be needed to establish a founder effect for either variant.

270 Of the four previously unreported variants, *TTC8* c.1214T>A and *EHMT1* c.981+1G>C are
271 predicted loss-of-function variants in genes in which loss of function is an established disease
272 mechanism, while *ARL6* p.(Ser62Cys) and the in-frame *MC4R* insertion were homozygous in
273 affected children and heterozygous in their parents.

274 A molecular diagnosis had direct consequences for care. Bardet–Biedl and Alström
275 syndromes require renal and ophthalmological surveillance, and Alström syndrome
276 cardiological surveillance; one child in our cohort had dilated cardiomyopathy [6, 8].

277 Setmelanotide is authorized in Europe for genetically confirmed Bardet–Biedl syndrome and
278 biallelic loss-of-function *LEPR* deficiency [35]; eligibility cannot be inferred for the two
279 children with the *LEPR* VUS. In four families, a second affected sibling was identified,
280 which shows the value of family testing.

281 Strengths include multidisciplinary phenotyping, a stepwise strategy combining cytogenetic,
282 copy-number, repeat-expansion and sequence analysis, exome sequencing in most children
283 without a diagnosis, and segregation analysis where possible. Limitations include the

retrospective single-center design and the small number of events, which make the estimates imprecise and the regression analyses exploratory. Nine children without a finding did not undergo exome sequencing, so the yield may be underestimated. Consanguinity, onset and hyperphagia were taken from the clinical history, and consanguinity was missing for three children. Two findings rest on a *LEPR* VUS without functional confirmation. Finally, methylation analysis was not performed in the child with the 15q11.2–q13.1 deletion, so its parental origin was not demonstrated; the diagnosis of Prader–Willi syndrome rested on the deletion and a characteristic clinical course.

Conclusion

In children from eastern Türkiye selected for genetic evaluation of obesity, about one-third had a molecular finding, most commonly homozygous variants causing Bardet–Biedl syndrome, and parental consanguinity was the feature most strongly associated with a diagnosis. In populations with frequent consanguinity, the history should include parental relatedness, and testing should extend beyond *MC4R* to recessive ciliopathy and leptin–melanocortin pathway genes. Multicenter studies are needed to confirm these findings and to clarify the significance of the recurrent *LEPR* and *BBS1* variants.

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Data availability The data supporting the findings of this study are not publicly available because they contain information that could compromise participant privacy; de-identified

429 data are available from the corresponding author on reasonable request, subject to ethical and
430 institutional requirements.

431 **Ethics approval** This retrospective study was performed in line with the principles of the
432 Declaration of Helsinki. Approval was granted by the Non-Interventional Clinical Research
433 Ethics Committee of the University of Health Sciences, Van Training and Research Hospital
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435 **Consent to participate** Written informed consent was obtained from the parents or legal
436 guardians of all children included in the study.

437 **Consent to publish** The parents or legal guardians consented to the publication of de-
438 identified clinical and genetic data. No identifying images are included.

Table 1 Demographic, anthropometric, clinical and laboratory characteristics at first evaluation, according to molecular finding status

Characteristic	Overall (n = 45)	Molecular finding (n = 16)	No molecular finding (n = 29)	p value
Demographic and anthropometric characteristics				
Age at first evaluation, years	7.12 ± 4.03	5.19 ± 3.66	8.19 ± 3.88	0.015
Sex, male, n (%)	23 (51.1)	8 (50.0)	15 (51.7)	0.912
Age at obesity onset, years (n = 44)	4.00 (1.00–5.00)	1.00 (0.60–4.00)	4.00 (2.00–5.12)	0.023
BMI SDS	3.40 (2.95–3.94)	3.54 (3.20–3.99)	3.33 (2.90–3.90)	0.420
Weight SDS	3.48 ± 1.46	3.57 ± 2.12	3.43 ± 0.98	0.807
Height SDS	0.15 (−0.31 to 0.86)	−0.08 (−0.33 to 0.21)	0.53 (−0.31 to 1.06)	0.073
Prepubertal (Tanner I), n (%)	36 (80.0)	14 (87.5)	22 (75.9)	0.456
Clinical features, n (%)				
Parental consanguinity (n = 42)	21 (50.0)	12/14 (85.7)	9/28 (32.1)	0.001
Obesity onset ≤5 years (n = 44)	35 (79.5)	14/16 (87.5)	21/28 (75.0)	0.450
Hyperphagia	34 (75.6)	15 (93.8)	19 (65.5)	0.067
Developmental delay	20 (44.4)	10 (62.5)	10 (34.5)	0.070
Dysmorphic features	16 (35.6)	9 (56.3)	7 (24.1)	0.031
Night eating	30 (66.7)	13 (81.3)	17 (58.6)	0.123
Parental obesity	15 (33.3)	4 (25.0)	11 (37.9)	0.378
Laboratory findings				
Fasting glucose, mg/dL (n = 42)	87.0 (82.0–93.8)	82.5 (81.0–89.3)	88.0 (85.0–93.8)	0.105
Fasting insulin, µIU/mL (n = 39)	14.5 (10.9–31.5)	14.8 (10.9–30.3)	14.5 (11.0–31.0)	0.803
HOMA-IR (n = 36)	3.20 (2.20–6.67)	2.30 (2.08–6.60)	3.45 (2.54–6.67)	0.383
HbA1c, % (n = 36)	5.65 (5.38–5.90)	5.85 (5.62–5.97)	5.50 (5.30–5.78)	0.035
ALT, U/L (n = 41)	22.0 (18.0–32.0)	28.0 (20.0–37.5)	21.0 (17.0–27.0)	0.092
Triglycerides, mg/dL (n = 37)	128.0 (82.0–173.0)	167.5 (128.0–179.5)	103.0 (77.5–148.5)	0.021
HDL-C, mg/dL (n = 38)	38.8 ± 10.8	36.8 ± 11.1	40.1 ± 10.6	0.365
LDL-C, mg/dL (n = 37)	93.4 ± 21.1	94.0 ± 20.0	93.0 ± 22.1	0.891
TSH, mIU/L (n = 38)	2.92 (2.41–4.17)	3.90 (2.41–4.35)	2.75 (2.40–3.50)	0.340
Free T4, ng/dL (n = 37)	1.20 ± 0.25	1.15 ± 0.23	1.23 ± 0.26	0.297

Data are mean ± SD, median (IQR) or n (%). The number of children with available data is shown when it was lower than the full cohort; for parental consanguinity and obesity onset, group denominators are given. p values were calculated with Welch's t test, the Mann–Whitney U test, the χ^2 test or Fisher's exact test, as appropriate. Laboratory comparisons were exploratory and were not adjusted for multiple testing. ALT, alanine aminotransferase; BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SDS, standard deviation score; TSH, thyroid-stimulating hormone

Table 2 Clinical and molecular characteristics of the 16 children with a molecular finding

Pt	Sex	Age first / last visit (y)	BMI SDS, first visit	Gene or locus (inheritance)	Variant	Zygoty	ACMG class (criteria)	ClinVar	Diagnosis (OMIM)	Diagnostic test	Parental testing	Parental consanguinity	Additional findings
P1	M	6.2 / 8.1	3.96	15q11.2–q13.1	6.1-Mb deletion chr15:22651951-28733793 (hg38)	Het	P	–	Prader–Willi syndrome (#176270)	CMA, MLPA	Not tested	No	ID, cryptorchidism, neonatal hypotonia and feeding difficulties
P2	M	4.0 / 10.7	3.58	<i>BBS1</i> (AR)	c.48-3C>G p.?	Hom	LP (PM3, PM2, PP3, PP4)	Pathogenic	Bardet–Biedl syndrome 1 (#209900)	BBS gene panel	Not tested	No	Chronic kidney disease, PAP of the right hand
P3	F	5.9 / 9.8	3.35	<i>TTC8</i> (AR)	c.1214T>A p.(Leu405Ter)	Hom	LP (PVS1, PM2)	Not reported	Bardet–Biedl syndrome 8 (#615985)	CES	Both parents het	Distant	PAP of both hands and feet, chronic kidney disease, RP, history of hypotonia
P4	F	6.2 / 12.0	3.50	<i>TTC8</i> (AR)	c.1214T>A p.(Leu405Ter)	Hom	LP (PVS1, PM2)	Not reported	Bardet–Biedl syndrome 8 (#615985)	Familial variant	Both parents het	Distant	PAP of both hands and feet, RP, congenital hypothyroidism (sibling of P3)
P5	M	1.4 / 11.6	2.97	<i>ARL6</i> (AR)	c.184A>T p.(Ser62Cys)	Hom	LP (PM2, PP1, PP2, PP3, PP4)	Not reported	Bardet–Biedl syndrome 3 (#600151)	CES	Both parents het	First cousins	ID, RP, hypogonadism, cryptorchidism, congenital hypothyroidism
P6	F	5.2 / 11.6	3.27	<i>ARL6</i> (AR)	c.184A>T p.(Ser62Cys)	Hom	LP (PM2, PP1, PP2, PP3, PP4)	Not reported	Bardet–Biedl syndrome 3 (#600151)	Familial variant	Both parents het	First cousins	History of DD, RP (sibling of P5)
P7	M	11.3 / 13.3	4.07	<i>BBS1</i> (AR)	c.48-3C>G p.?	Hom	LP (PM3, PM2, PP3, PP4)	Pathogenic	Bardet–Biedl syndrome 1 (#209900)	CES	Both parents het	Second cousins	RP, ureteropelvic junction obstruction, PAP of the feet, autism spectrum disorder, learning difficulties, cryptorchidism
P8	M	0.6 / 6.7	2.75	<i>MC4R</i> (AD, AR)	c.378C>A p.(Asp126Glu)	Hom	LP (PP1, PM1, PP2, PM2)	Not reported ^a	Obesity due to MC4R deficiency (#618406)	<i>MC4R</i> sequencing	Not tested	First cousins	–
P9	F	6.8 / 17.8	3.78	<i>MC4R</i> (AD, AR)	c.378C>A p.(Asp126Glu)	Hom	LP (PP1, PM1, PP2, PM2)	Not reported ^a	Obesity due to MC4R deficiency (#618406)	<i>MC4R</i> sequencing	Not tested	First cousins	Congenital hypothyroidism (sibling of P8)
P10	F	1.0 / 5.0	4.65	<i>MC4R</i> (AD, AR)	c.232_233insGAA p.(Pro78delinsArgThr)	Hom	LP (PM2, PM4, PM1)	Not reported	Obesity due to MC4R deficiency (#618406)	CES	Both parents het	First cousins	–
P11	F	0.5 / 1.3	8.54	<i>LEPR</i> (AR)	c.1938G>T p.(Trp646Cys)	Hom	VUS (PP3, PM1, PM2)	Not reported ^a	Leptin receptor deficiency (#614963)	CES	Both parents het	First cousins	–
P12	F	2.0 / 10.4	6.43	<i>LEPR</i> (AR)	c.1938G>T p.(Trp646Cys)	Hom	VUS (PP3, PM1, PM2)	Not reported ^a	Leptin receptor deficiency (#614963)	CES	Not tested	Not recorded	Hypothyroidism
P13	M	5.0 / 6.5	2.32	<i>ALMS1</i> (AR)	c.6828C>A p.(Cys2276Ter)	Hom	P (PVS1, PP5, PM2)	P/LP	Alström syndrome (#203800)	<i>ALMS1</i> sequencing	Both parents het	First cousins	Dilated cardiomyopathy; normal intellect, attends kindergarten
P14	M	5.4 / 14.2	2.73	<i>ALMS1</i> (AR)	c.6828C>A p.(Cys2276Ter)	Hom	P (PVS1, PP5, PM2)	P/LP	Alström syndrome (#203800)	<i>ALMS1</i> sequencing	Both parents het	First cousins	RP, hyperinsulinemia, hyperlipidemia, increased renal medullary echogenicity, ID (special education) (sibling of P13)
P15	F	12.9 / 16.8	3.65	<i>EHMT1</i> (AD)	c.981+1G>C p.?	Het	LP (PVS1, PM2)	Not reported	Kleefstra syndrome 1 (#610253)	WES	Not tested	Not recorded	Down-like facial features, ID, behavioral abnormalities, peripheral pulmonary stenosis
P16	M	8.7 / –	3.31	<i>FMRI</i> (XL)	>200 CGG repeats	Hemi	Full mutation	–	Fragile X syndrome (#300624)	<i>FMRI</i> CGG-repeat PCR	Mother: 30/98 CGG repeats (premutation)	Yes (degree not recorded)	ID, autism spectrum disorder, hyperphagia, self-injurious behavior

Age and BMI SDS at first visit correspond to the data in Table 1; age at last visit is given because additional findings were recorded up to that visit. ^aNot reported in ClinVar, but previously described in the literature. AD, autosomal dominant; AR, autosomal recessive; BBS, Bardet–Biedl syndrome; CES, clinical exome sequencing; CMA, chromosomal microarray analysis; DD, developmental delay; F, female; Hemi, hemizygous; Het, heterozygous; Hom, homozygous; ID, intellectual disability; LP, likely pathogenic; M, male; MLPA, multiplex ligation-dependent probe amplification; P, pathogenic; PAP, postaxial polydactyly; Pt, patient; RP, retinitis pigmentosa; VUS, variant of uncertain significance; WES, whole-exome sequencing; XL, X-linked

Table 3 Logistic regression analyses of features associated with a molecular finding

Variable	n	Univariable OR (95% CI)	p value	Model 1 aOR (95% CI) n = 44; 16 events	Model 2 aOR (95% CI) n = 42; 14 events
Parental consanguinity	42	12.67 (2.33–68.93)	0.003	–	6.64 (1.05–41.80) p = 0.044
Age at obesity onset, per 1-year increase	44	0.72 (0.53–0.98)	0.040	0.62 (0.42–0.91) p = 0.014	0.73 (0.48–1.10) p = 0.134
Dysmorphic features	45	4.04 (1.10–14.88)	0.036	8.41 (1.58–44.83) p = 0.013	4.66 (0.82–26.57) p = 0.083
Developmental delay	45	3.17 (0.89–11.27)	0.075	–	–
Hyperphagia	45	7.89 (0.91–68.75)	0.061	–	–
Parental obesity	45	0.55 (0.14–2.12)	0.382	–	–

Univariable analyses used all available data. Model 1 included age at obesity onset and dysmorphic features; model 2 additionally included parental consanguinity. Both models were fitted in children with complete data for the included variables. Given the small number of events, the models are exploratory. aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

Figure legends

Fig. 1 Flow of the study cohort, stepwise genetic testing strategy and spectrum of molecular findings. BMI, body mass index; CMA, chromosomal microarray analysis; MLPA, multiplex ligation-dependent probe amplification; SDS, standard deviation score; VUS, variant of uncertain significance

