THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Obesity

Obesity occurs when abnormal amounts of triglycerides are stored in adipose tissuse and released as free fatty acids with detrimental effects [1]. Dietary and lifestyle factors, and epigenetic modifications play a role in excess fat accumulation. Obesity is correlated with an increased risk of type-2-diabetes, cardiovascular disease, cancer and mortality [1]. Obesity can be found as an isolated clinical finding as well as part of a mutli-systemic syndromic diagnosis.

Our Monogenic Obesity Panel includes analysis of all 38 genes listed below.

Monogenic obesity	Bardet-Biedl Syndrome			Prader-Willi like	Other	
MC4R	BBS1	TTC8 (BBS8)	MKS1 (BBS13)	MAGEL2	AFF4	PHF6
LEP	BBS2	BBS9	CEP290 (BBS14)	SIM1	ALMS1	PRMT7
LEPR	ARL6 (BBS3)	BBS10	WDPCP (BBS15)		CUL4B	SETD2
POMC	BBS4	TRIM32 (BBS11)	SDCCAG8 (BBS16)		GNAS	VPS13B
NR0B2	BBS5	BBS12			KIDINS220	
DYRK1B	MKKS (BBS6)	IFT172			NTRK2	
UCP3	BBS7	IFT74			PCSK1	

Our Non-Syndromic Monogenic Obesity Panel includes analysis of all 7 genes listed below.

Non-Syndromic Monogenic Obesity					
DYRK1B	LEP	LEPR	MC4R	NR0B2	POMC
UCP3					

Monogenic obesity

Gene	Clinical Features	Details
MC4R, LEP, LEPR, POMC	Monogenic obesity	Heterozygous mutations in the *MC4R*, *LEP*, *LEPR*, and *POMC* genes are identified in patients with obesity. Phenotypes are non-fully penetrant. *MC4R* mutations are the most common, with a population prevalence of at least 0.05% and a prevalence of 0.5%–1% among obese adults and 1%–6% among obese children [2].
DYRK1B	Central obesity, diabetes, hypertension	A heterozygous variant in the *DYRK1B* gene has been identified in 3 unrelated Iranian families with early onset coronary artery disease and/or myocardial infarction, juvenile onset central obesity, type 2 diabetes, and hypertension [3].
NR0B2	Obesity, mild, early onset	Mutations in *NR0B2* were initially identified in Japanese subjects (6 out of 173) with early-onset diabetes and mild to moderate obesity. Additional screening of 101 non-diabetic subjects with early onset obesity identified mutations in 6 additional individuals. [4].
UCP3	Monogenic obesity	Heterozygous mutations in the *UCP3* gene have been identified in individuals with childhood onset obesity [5]. Compound heterozygous variants have also been reported in association with morbid obesity and diabetes [6].

Bardet-Biedl Syndrome

Gene	Clinical Features	Details
BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, IFT172, IFT74, MKS1 (BBS13), CEP290 (BBS14), WDPCP	Bardet-Biedl syndrome	Bardet-Biedl syndrome (BBS) is an autosomal recessive multi-systemic ciliopathy characterized by retinal dystrophy, obesity, postaxial polydactyly, leaning difficulties, renal involvement and genitourinary abnormalities [7]. Mutations in 16 *BBS* genes (*BBS1* through *BBS16*) account for approximately 80% of clinically diagnosed BBS patients [8]. In individuals of European and Caucasian ancestry, the majority of mutations are identified in *BBS1* and *BBS10* which account for 23% and 20% of identified mutations, respectively [8].

(BBS15), SDCCAG8 (BBS16)		

Prader-Willi like syndrome

Gene	Clinical Features	Details
MAGEL2	Prader-Willi syndrome	Prader-Willi syndrome (PWS)] is a genetic disorder which causes hypotonia and poor feeding in infancy, followed by the development of hyperphagia and subsequent obesity. *De novo* truncating mutations in the paternally inherited copy of *MAGEL2* have been associated with classic PWS or PWS-like features [9]. The proportion of PWS associated with *MAGEL2* mutations is unknown, but is predicted to be low.
SIM1	Prader-Willi like syndrome	Loss of function missense mutations in *SIM1* have been identified in patients with severe obesity associated with, or independent of, Prader-Willi-like features [10].

Other

Gene	Clinical Features	Details
AFF4	CHOPS syndrome	Heterozygous de novo variants in *AFF4* have been described in patients with CHOPS syndrome, which is characterized by cognitive impairment, coarse facies, heart defects, obesity, pulmonary involvement, short stature, and skeletal dysplasia [11].
ALMS1	Alstrom syndrome	Alstrom syndrome [OMIM#203800] is characterized by progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, dilated or restrictive cardiomyopathy and childhood obesity. Type 2 diabetes mellitus is observed in nearly all patients before the second decade [12]. Homozygous or compound heterozygous mutations in the *ALMS1* gene cause Alström syndrome [13]. The majority of mutations identified to date are nonsense and frameshift that are predicted to cause premature protein truncation [14].
CUL4B	X-linked intellectual disability, syndromic-15 (Cabezas type)	Hemizygous variants in the *CUL4B* gene have been associated with X-linked intellectual disability. During adolescence, affected males typically develop central obesity, and have delayed puberty, hypogonadism, relative macrocephaly and moderate short stature [15].
GNAS	Pseudo-hypoparathroidism (PHP) and pseudo-pseudo-hypoparathyroidism (PPHP)	PHP Ia is associated with a constellation of clinical features referred to as Albright hereditary osteodystrophy (AHO), which includes short stature, obesity, round facies, subcutaneous ossifications, brachydactyly, and other skeletal anomalies. PPHP is characterized by the physical findings of AHO but without hormone resistance. Heterozygous inactivating *GNAS* mutations lead to either PHP-Ia, when maternally inherited, or PPHP, if paternally inherited. *GNAS* mutations are detected in 60-70% of affected subjects, most patients/families harbor private mutations and no genotype-phenotype correlation has been found to date [16].
KIDINS220	SINO syndrome	Heterozygous variants in *KIDINS220* have been associated with SINO (Spastic paraplegia, Intellectual disability, Nystagmus, and Obesity) [17].
NTRK2	Obesity, hyperphagia, and developmental delay	A heterozygous de-novo missense mutation in *NTRK2* was identified in a male patient with early-onset obesity, hyperphagia and severe developmental delay [18].
PCSK1	Obesity with impaired prohormone processing	Homozygous or compound heterozygous mutations in *PCSK1* have been identified in patients with early onset obesity, hyperphagia, reactive hypoglycemia, and (entero)endocrine dysfunctions [19]. Common variants in *PCSK1* also have been associated with obesity in heterozygotes in several population-based studies.
PHF6	Borjeson-Forssman-Lehmann syndrome	Borjeson-Forssman-Lehmann syndrome is characterized by moderate to severe intellectual disability, epilepsy, hypogonadism, hypometabolism, obesity with marked gynecomastia, swelling of subcutaneous tissue of the face, narrow palpebral fissure and large ears [20]. Mutations in *PHF6* have been identified in patients with Borjeson-Forssman-Lehmann syndrome. Female carriers are typically mildly affected or not affected at all.
PRMT7	Short stature, bracydactyly, intellectual disability and seizures	Biallelic mutations in *PRMT7* have been associated with SBIDDS (short stature, bracydactyly, intellectual disability and seizures). Affected individuals are typically also obese [21].
SETD2	Luscan-Lumish syndrome	Heterozygous mutations in *SETD2* are associated with Luscan-Lumish syndrome, macrocephaly, intellectual disability, speech delay, low sociability, and behavioral problems. Affected individuals may also have postnatal overgrowth and obesity [22].

VPS13B	Cohen syndrome	Cohen syndrome is a rare autosomal recessive disorder with a variable clinical picture mainly characterized by developmental delay, mental retardation, microcephaly, typical facial dysmorphism, progressive pigmentary retinopathy, severe myopia, and intermittent neutropenia [23]. Truncal obesity develops in mid-childhood. Homozygous and compound heterozygous mutations in *VPS13B* have been identified in patients with Cohen syndrome.

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Monogenic Obesity Panel (38 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3000
CPT codes:	81406 81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Non-Syndromic Monogenic Obesity Panel (7 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2500
CPT codes:	81406 81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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