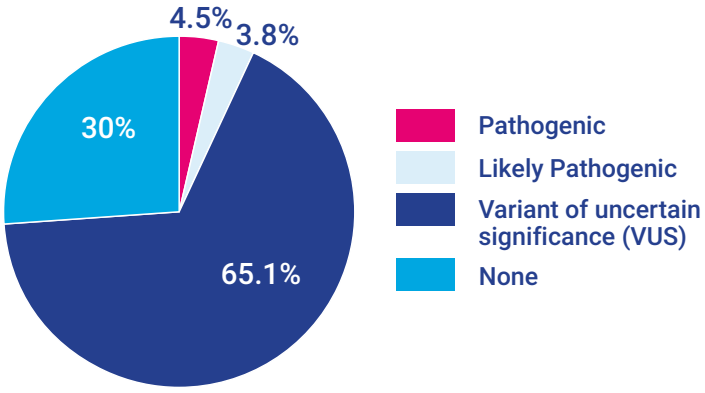
Are you aware of the frequency of obesity-associated gene variants?

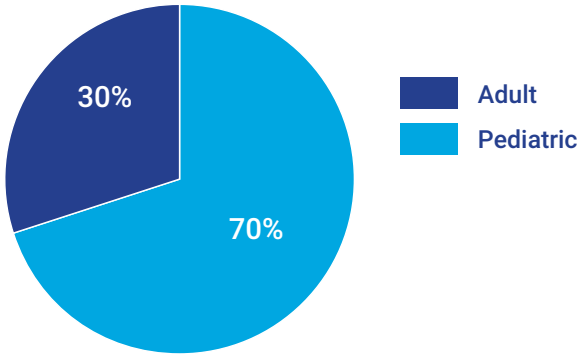
It is likely that the true prevalence of rare genetic diseases of obesity has previously been underestimated because genetic testing is often not done in individuals with obesity, both pediatric and adult.

Sequences from 54,570 individuals were tested using the Uncovering Rare Obesity® Program, including by the expanded 87-gene and 1–chromosomal region panel

While individual gene variants are rare, spotting one in the MC4R pathway is surprisingly common. Since the beginning of this testing program, ~1,556 (2.85%) individuals with positive results have been identified as having pathogenic or likely pathogenic variants that also met the mode of inheritance.[a]



70% of individuals had at least 1 pathogenic variant, likely pathogenic variant, or variant of uncertain significance in one of the 87 genes.[b]

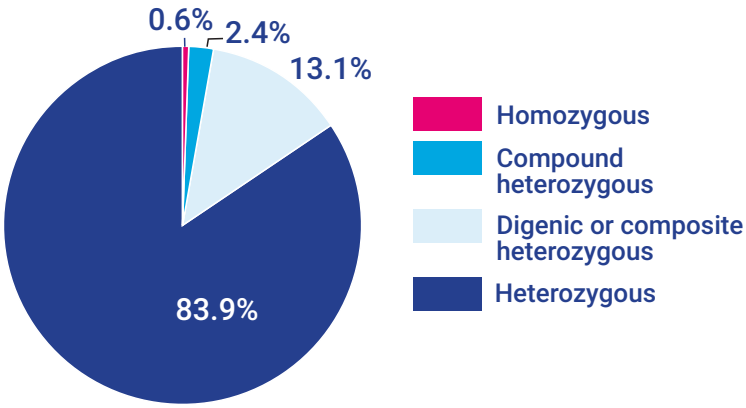


30% of all positive test results are in adults. While pediatric testing is essential, it is equally important to ensure that adults are tested.

Most frequent positive results

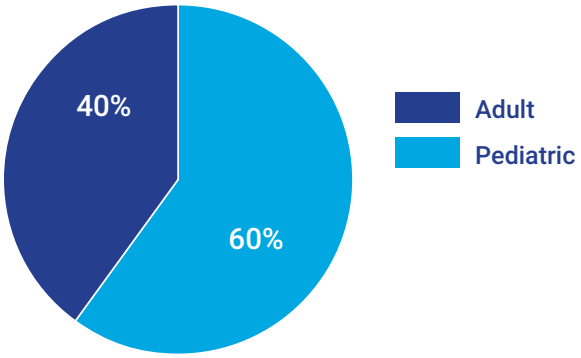
MC4R – 52.8%	*GNAS* – 3.4%	*MAGEL2* – 1.9%	*MECP2* – 1.2%
SH2B1 – 16.2%	*RAI1* – 2.7%	*PROK2* – 1.9%	*SIM1* – 1.2%
BBSx – 6.7%[c]	*KSR2* – 2.1%	*PHIP* – 1.7%	*LEPR* – 1.0%

Since the beginning of this testing program, 14,450 individuals had a test result with a variant in a Bardet-Biedl Syndrome (BBS) associated gene.[c] 440 (3%) of them had biallelic (i.e., homozygous or compound heterozygous) BBS variants.



~84% had a heterozygous variant in one of the BBS genes including pathogenic, likely pathogenic or VUS.

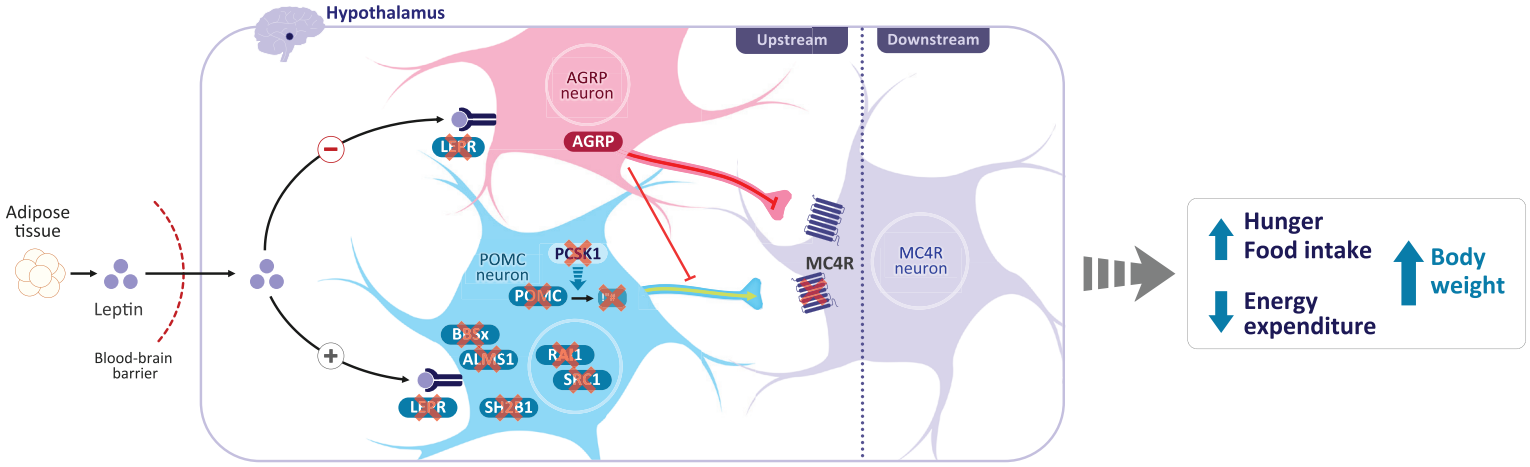
~16% had a homozygous, compound heterozygous, or digenic variant in a BBS gene.



40% of BBS positive test results are in adults.

[a]Mode of inheritance criteria were defined as ≥2 alleles in autosomal recessive conditions or ≥1 allele in autosomal dominant conditions.
[b]Patients may have >1 variant and therefore may be represented in >1 section of the pie charts.
[c]Panel includes 29 BBS-associated genes.

Rare genetic variants can result in the impairment of the MC4R Pathway



For a complete list of genes tested, see table below.

Uncovering Rare Obesity® is a no-charge*, genetic testing program for rare genetic diseases of obesity sponsored by Rhythm Pharmaceuticals, Inc.

To be eligible for testing through the Uncovering Rare Obesity® program, patients must be located in the United States or its territories, or Canada, and:

- ≤18 years of age with body mass index (BMI) ≥97th percentile, OR
- ≥19 years of age with BMI ≥40 kg/m2 and a history of childhood obesity, OR
- an immediate family member of select, previously tested patients, OR
- showing clinical symptoms of Bardet-Biedl syndrome (BBS)

*Rhythm Pharmaceuticals covers the cost of the test and provides sample collection kits. Patients are responsible for any office visit, sample collection, or other costs.

Uncovering Rare Obesity® panel

						Bardet-Biedl Syndrome-Associated Genes		
ADCY3	EP300	MC3R	PCSK1	RAB23	SEMA3G	ARL6 (BBS3)	CFAP418 (BBS21)	NPHP1
AFF4	GNAS	MC4R	PHF6	RAI1	SH2B1	BBIP1 (BBS18)	CEP164	SCAPER
ALMS1	HTR2C	MECP2	PHIP	RPGRIP1L	SIM1	BBS10	CEP290 (BBS14)	SCLT1
ASIP	INPP5E	MRAP2	PLXNA1	RPS6KA3	TBX3	BBS12	IFT172 (BBS20)	SDCCAG8 (BBS16)
BDNF	ISL1	NCOA1 (SRC1)	PLXNA2	SEMA3A	TRPC5	BBS1	IFT27 (BBS19)	TMEM67
CPE	KIDINS220	NROB2	PLXNA3	SEMA3B	TUB	BBS2	IFT74 (BBS22)	TRIM32 (BBS11)
CREBBP	KSR2	NRP1	PLXNA4	SEMA3C	UCP3	BBS4	LRRC45	TTC8 (BBS8)
CUL4B	LEP	NRP2	POMC	SEMA3D	VPS13B	BBS5	LZTFL1 (BBS17)	TTC21B
DNMT3A	LEPR	NTRK2	PPARG	SEMA3E		BBS7	MKKS (BBS6)	WDPCP (BBS15)
DYRK1B	MAGEL2	PCNT	PROK2	SEMA3F		BBS9 (PTHB1)	MKS1 (BBS13)	

Chromosome 16p11.2 region

Rhythm® PHARMACEUTICALS