Frequency of *BBS* and *ALMS1* Variants in a Cohort With Early-Onset Obesity

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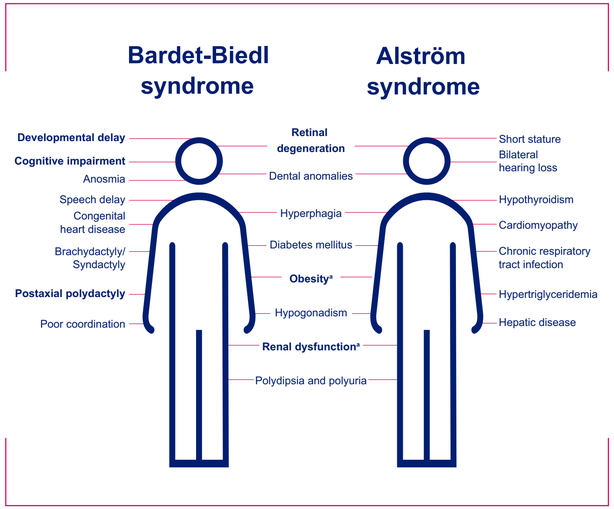
Summary

- **Biallelic variants in genes related to Bardet-Biedl syndrome (BBS) or Alström syndrome were identified in 1.4% of patients in a large cohort of individuals with early-onset, severe obesity**
- **Additional evidence to support the clinical diagnosis of BBS and Alström syndrome may be provided through genetic testing**

Introduction

- The rare autosomal recessive syndromes BBS and Alström syndrome are believed to arise from dysfunction of primary cilia leading to characteristic traits of early-onset, severe obesity and hyperphagia[1-3]
- Diagnoses of BBS and Alström syndrome are based on clinical features; common features between the syndromes are obesity, diabetes mellitus, visual impairment, and renal anomalies, whereas other features are distinct (Figure 1)[1,2,4]
- BBS is associated with variants in >20 genes; Alström syndrome is associated with variants in *ALMS1*[1,5]
- Confirmation of clinical diagnosis in patients with syndromic obesity may be supported by genetic testing[2,6]
- In individuals with severe, early-onset obesity, the frequency of variants in genes related to BBS and Alström syndrome irrespective of clinical features requires further investigation

Figure 1. Bardet-Biedl syndrome and Alström syndrome clinical characteristics.[2-4,7,8]



Primary features for clinical diagnosis of each syndrome are shown in bold, unless otherwise noted. [a]Primary clinical diagnostic features of Bardet-Biedl syndrome; minor criteria for diagnosis of Alström syndrome.

Objective

- To assess the frequency of variants in genes related to BBS and Alström syndrome through the Uncovering Rare Obesity® genetic testing program

Methods

Design of the Uncovering Rare Obesity® program

- The Uncovering Rare Obesity® program began in May 2019 and uses a panel of 79 genes and 1 chromosomal region related to obesity (Table)

Table. Uncovering Rare Obesity® Genetic Panel–Included Genes and Regions

BBS- or Alström syndrome–associated genes			
ALMS1	*ARL6 (BBS3)*	*BBIP1 (BBS18)*	*BBS1*
BBS10	*BBS12*	*BBS2*	*BBS4*
BBS5	*BBS7*	*BBS9 (PTHB1)*	*C8ORF37 (BBS21)*
CEP290 (BBS14)	*IFT172*	*IFT27 (BBS19)*	*IFT74 (BBS20)*
LZTFL1 (BBS17)	*MKKS (BBS6)*	*MKS1 (BBS13)*	*SDCCAG8 (BBS16)*
TRIM32 (BBS11)	*TTC8 (BBS8)*	*WDPCP (BBS15)*	
Non–BBS- or non-Alström syndrome–associated genes or regions			
ADCY3	*BDNF*	*GNAS*	*KSR2*
LEP	*LEPR*	*MC3R*	*MC4R*
NCOA1 (SRC1)	*NTRK2*	*PCSK1*	*PHF6*
POMC	*RAI1*	*SH2B1*	*SIM1*
CPE	*AFF4*	*CREBBP*	*CUL4B*
DNMT3A	*DYRK1B*	*EP300*	*HTR2C*
INPP5E	*ISL1*	*KIDINS220*	*MAGEL2*
MECP2	*MRAP2*	*NR0B2*	*NRP1*
NRP2	*PCNT*	*PHIP*	*PLXNA1*
PLXNA2	*PLXNA3*	*PLXNA4*	*PPARG*
PROK2	*RAB23*	*RPGRIP1L*	*RPS6KA3*
SEMA3A	*SEMA3B*	*SEMA3C*	*SEMA3D*
SEMA3E	*SEMA3F*	*SEMA3G*	*TBX3*
TRPC5	*TUB*	*UCP3*	*VPS13B*
16p11.2[a]			

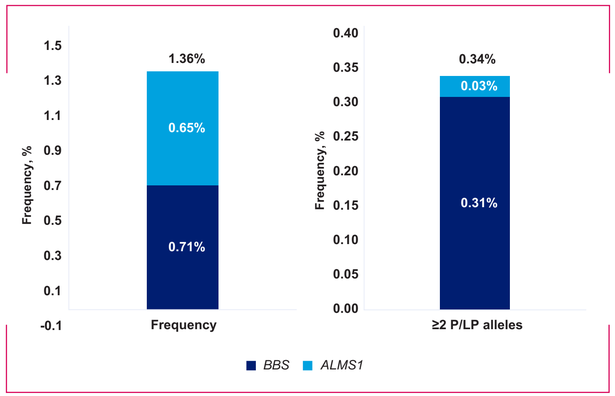
[a]Assessment for rearrangement of the 16p11.2 chromosomal region.

- Individuals within the United States and its territories and Canada may be eligible to receive a no-charge genetic test and 2 genetic counseling sessions if they
  - Are ≤18 years of age and have a body mass index ≥97th percentile, or
  - Are ≥19 years of age and have a body mass index ≥40 kg/m^2 with a history of childhood obesity, or
  - Are a relative of someone previously tested, or
  - Show clinical symptoms related to BBS
- Blood or buccal samples submitted for testing are performed by a Clinical Laboratory Improvement Amendments–accredited laboratory

Frequency analysis

- Individuals with severe obesity had tests submitted to the Uncovering Rare Obesity® program and were sequenced for 22 BBS-associated genes and *ALMS1*
- Variants were classified as pathogenic/likely pathogenic or as a variant of uncertain significance on the basis of American College of Medical Genetics criteria
- Resulting variants identified in individuals were categorized as biallelic (≥2 alleles in 1 gene; includes homozygous or compound heterozygous) or heterozygous (1 allele in 1 gene)
  - Haplotype analysis was used to remove predicted *cis* compound heterozygous variants from the biallelic count

Figure 2. Frequency of biallelic *BBS* and *ALMS1* variants in a cohort of individuals with early-onset, severe obesity (N=13,857).



P/LP, pathogenic/likely pathogenic.

Results

- Sequences from 13,857 individuals with early-onset, severe obesity were analyzed
- Data on clinical characteristics other than early-onset, severe obesity and details on whether individuals had genes sequenced because of suspected syndromic obesity were not available
- Biallelic *BBS* or *ALMS1* variants were found in 1.36% of individuals tested (Figure 2)
  - Variants in BBS-associated genes were identified in 0.71% of individuals
  - *ALMS1* variants were identified in 0.65% of individuals
  - Of individuals tested, 0.34% had ≥2 pathogenic/likely pathogenic alleles (*BBS*: 0.31%; *ALMS1*: 0.03%)

Conclusions

- Biallelic variants in BBS-associated genes or *ALMS1* were identified in 1.4% of the 13,857 individuals sequenced as part of the Uncovering Rare Obesity® program
- Given the heterogeneous nature, multitude of symptoms, and varied clinical presentations associated with BBS and Alström syndrome, continued research is necessary to identify biallelic variants that might assist in diagnosing individuals with these syndromes
- More information about the Uncovering Rare Obesity® testing program can be found at uncoveringrareobesity.com
- A similar program, Rare Obesity Advanced Disease (ROAD) is available in the EU; more information is available at https://www.roadgenetic.unilabsweb.com/

LEARN MORE ABOUT THE UNCONVERING RARE OBESITY® PROGRAM

Visit the new website
UncoveringRareObesity.com
your new destination to order kits, view results, and access educational materials.

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