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

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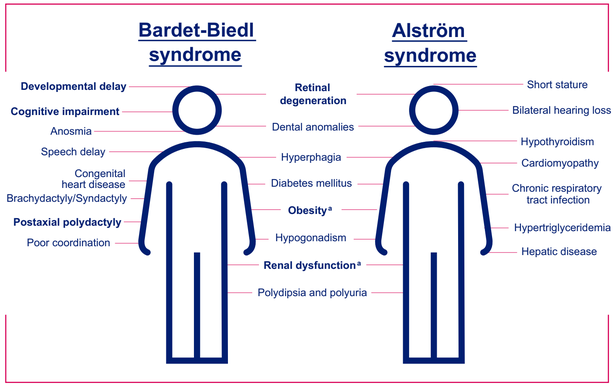
Summary

- **In a large cohort of individuals with early-onset, severe obesity, biallelic variants in genes associated with Bardet-Biedl syndrome (BBS) or Alström syndrome were identified in 1.96% of individuals**
- **Genetic testing may provide additional evidence to support the clinical diagnosis of individuals with BBS and Alström syndrome**

Introduction

- BBS and Alström syndrome are rare autosomal recessive syndromes characterized by early-onset, severe obesity and hyperphagia; evidence suggests dysfunction of primary cilia plays a key role in both syndromes[1-3]
- Both BBS and Alström syndrome are diagnosed on the basis of clinical features; some common clinical features are similar between the syndromes, including obesity, diabetes mellitus, visual impairment, and renal anomalies, while others are distinct (Figure 1)[1,2,4]
- Variants in >20 genes are associated with BBS; variants in *ALMS1* are associated with Alström syndrome[1,5]
- Genetic testing may aid in or confirm the clinical diagnosis of patients with syndromic obesity[2,6]
- The frequency of variants in genes associated with BBS and Alström syndrome in individuals with severe, early-onset obesity irrespective of clinical features is unknown

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



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

Objectives

- To evaluate the frequency of variants in BBS- and Alström syndrome–associated genes in individuals tested as part of the Uncovering Rare Obesity® genetic testing program

Methods

Uncovering Rare Obesity® Program

- Uncovering Rare Obesity® was launched in May 2019 with a 40-gene panel of obesity-associated genes; the panel was expanded in July 2021 to include 79 genes and 1 chromosomal region (Table)
- Individuals may be eligible to receive a no-charge genetic test and 2 genetic counseling sessions if they are located in the United States and its territories, and
  - Are ≤18 years of age with body mass index ≥97th percentile, or
  - Are ≥19 years of age with body mass index ≥40 kg/m^2 and have a history of childhood obesity, or
  - Have a select family member who was previously tested
  - Show clinical symptoms of BBS
- Samples are collected via blood or buccal swab; tests are evaluated by a Clinical Laboratory Improvement Amendments–accredited laboratory

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..

Frequency Analysis

- 22 BBS-associated genes and *ALMS1* were sequenced in individuals with severe obesity who had tests submitted to the Uncovering Rare Obesity® program
- Variants were classified on the basis of the American College of Medical Genetics criteria as pathogenic/likely pathogenic (P/LP) or as a variant of uncertain significance (VUS)
- Individuals were determined to have biallelic (≥2 alleles in 1 gene), heterozygous (1 allele in 1 gene), or composite heterozygous (1 allele per gene in multiple genes) variants

Results

- Sequences of 8,459 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
- In this cohort, 1.96% of individuals were biallelic for *BBS* or *ALMS1* variants, 26.80% carried heterozygous variants in a single gene, and 4.00% were composite heterozygous (Figure 2)
  - Biallelic *BBS* and *ALMS1* variants were identified in 1.36% and 0.60% of individuals, respectively
  - 0.34% of those with biallelic variants had ≥2 P/LP alleles (*BBS*: 0.30%; *ALMS1*: 0.04%); after excluding individuals from a known BBS specialty clinic, this frequency was 0.24% (Figure 3)
  - 1.62% of individuals had biallelic variants with ≥1 VUS allele

Conclusions

- Among 8,459 individuals sequenced as part of the Uncovering Rare Obesity® program, 1.96% had biallelic variants in BBS-associated genes or *ALMS1*
- BBS and Alström syndrome are heterogeneous diseases characterized by multiple evolving symptoms; more research is needed to determine if identification of individuals with biallelic variants may help identify and diagnose individuals with these syndromes

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References: 1. Geets et al. *Clin Genet*. 2019;95:23-40. **2.** Marshall et al. *Eur J Hum Genet*. 2007;15:1193-1202. **3.** Sherafat-Kazemzadeh et al. *Pediatr Obes*. 2013;8:e64-e67. **4.** Beales et al. *J Med Genet*. 1999;36:437-446. **5.** Lindstrand et al. *Am J Hum Genet*. 2016;99:318-336. **6.** Forsythe et al. *Eur J Hum Genet*. 2013;21:8-13. **7.** Forsythe et al. *Front Pediatr*. 2018;6:23. **8.** Marshall et al. *Curr Genomics*. 2011;12:225-235.

Figure 2. Frequency of biallelic, heterozygous, and composite heterozygous variants in BBS-associated genes and *ALMS1* in a cohort of individuals with early-onset, severe obesity.

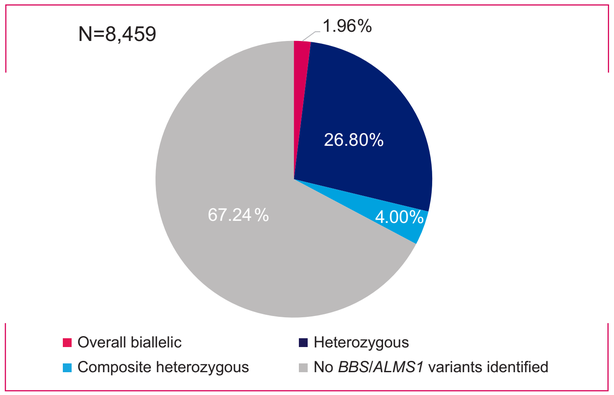
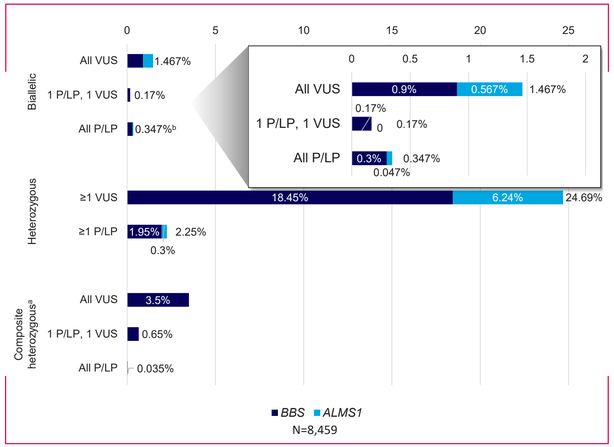


Figure 3. Comparison of *BBS* or *ALMS1* biallelic, heterozygous, and composite heterozygous genotypes in a cohort of individuals with early-onset, severe obesity.



Inset shows detailed comparison of *BBS* and *ALMS1* biallelic variants. [a]Composite heterozygous variants evaluated in BBS-associated genes only. [b]Overall frequency of 0.24% after excluding individuals from a known BBS specialty clinic. BBS, Bardet-Biedl syndrome; P/LP, pathogenic/likely pathogenic; VUS, variant of uncertain significance.