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GBE1 Adult Polyglucosan Body Disease

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Summary

Clinical characteristics

Most individuals with classic *GBE1* adult polyglucosan body disease (*GBE1*-APBD) present after age 40 years with unexplained progressive neurogenic bladder, gait difficulties (i.e., spasticity and weakness) from mixed upper and lower motor neuron involvement, sensory loss predominantly in the distal lower extremities, autonomic dysfunction (associated with orthostatic hypotension and constipation), and mild cognitive difficulties (often executive dysfunction). Some affected individuals without classic *GBE1*-APBD have atypical phenotypes including Alzheimer disease-like dementia and axonal neuropathy, stroke-like episodes, and diaphragmatic failure; others may have a history of infantile liver disease.

Diagnosis/testing

The diagnosis of *GBE1*-APBD is established in a proband with suggestive findings and biallelic *GBE1* pathogenic variants identified by molecular genetic testing. Note: GBE enzyme assay (in any tissue) is not a first-line diagnostic test for *GBE1*-APBD.

Management

Treatment of manifestations: Optimally, symptomatic care is provided by a multidisciplinary team that includes specialists in physical medicine rehabilitation, urology, and behavioral neurology or psychology. An individualized physical therapy program can improve flexibility, reduce spasticity, maintain or improve joint mobility, and facilitate activities of daily living; antispasmodic drugs may decrease cramps and facilitate walking. Spastic bladder may be managed with anticholinergic drugs and clean intermittent catheterization or an indwelling bladder catheter to prevent urosepsis; treatment of recurrent urinary infections is essential. Treatment of cognitive decline and psychiatric manifestations is per standard practice.

Surveillance: Routine: neurologic assessments to monitor progression of upper motor neuron and lower motor neuron signs and to assess for new manifestations; urologic evaluations for complications of spastic bladder;

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occupational and physical therapy assessments regarding activities of daily living; and mental health assessments.

Genetic counseling

GBE1-APBD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *GBE1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic heterozygote (carrier), and a 25% chance of being unaffected and not a carrier.

Once the *GBE1* pathogenic variants have been identified in the family, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing for *GBE1*-APBD are possible.

Diagnosis

Suggestive Findings

GBE1 adult polyglucosan body disease (*GBE1*-APBD) **should be considered** in individuals with the following clinical findings, neuroimaging findings, family history, and ethnicity.

Clinical findings

- Onset age ≥40 years
- Progressive neurogenic bladder
- Gait difficulties (i.e., spasticity and weakness) from mixed upper and lower motor neuron involvement
- Sensory loss predominantly in the distal lower extremities
- Mild difficulties in cognition (often executive dysfunction)
- A history of infantile liver disease [Paradas et al 2014]

Brain and spinal cord MRI

- Paraventricular, subcortical, and deep white matter slowly progressive changes that may include involvement of the upper pons, superior cerebellar peduncles, dentate nuclei, and anterior medulla (including the olives) often extending to the level of the cervical-medullary junction [Klein et al 2004]
- Cerebral, cerebellar, and spinal cord slowly progressive atrophy

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs (including sibs with infantile liver disease) and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Ethnicity is typically (but not necessarily) Ashkenazi Jewish.

Establishing the Diagnosis

The diagnosis of *GBE1*-APBD is established in a proband with suggestive findings and biallelic *GBE1* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1). GBE enzyme assay (in any tissue) is not a first-line diagnostic test for *GBE1*-APBD.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *GBE1* variants of uncertain significance (or of one known *GBE1* pathogenic variant and one *GBE1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (targeted analysis for pathogenic variants or multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas genomic testing does not (see Option 2).

Option 1

Targeted analysis for two *GBE1* pathogenic variants common in the Ashkenazi Jewish population can be performed first:

- p.Tyr329Ser [Lossos et al 1998]
- c.2053-5289_2053-5297delinsTGTTTTTTACATGACAGGT [Akman et al 2015]

A multigene panel that includes *GBE1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Sequence analysis. More than 90% of pathogenic variants are identified by sequence analysis.

Gene-targeted deletion/duplication analysis. More than 5% of pathogenic variants are identified by gene-targeted deletion/duplication analysis.

Table 1. Molecular Genetic Testing Used in *GBE1* Adult Polyglucosan Body Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GBE1	Sequence analysis [3]	>90% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	>5% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Note: Although almost all variants associated with *GBE1*-APBD to date are detectable by sequence analysis, the second most common variant, c.2053-5289_2053-5297delinsTGTTTTTTACATGACAGGT, is deep intronic and is unlikely to be detected by typical exon-targeted and splice junction-targeted sequencing assays [Akman et al 2015].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Intragenic deletions, such as those reported by Bruno et al [2004], Tay et al [2004], Raju et al [2008], and Li et al [2012] have been associated with glycogen storage disease type IV (see Genetically Related Disorders).

Clinical Characteristics

Clinical Description

Most individuals with *GBE1* adult polyglucosan body disease (*GBE1*-APBD) present after age 40 years with unexplained progressive neurogenic bladder, gait difficulties (i.e., spasticity and weakness) from mixed upper and lower motor neuron involvement, sensory loss predominantly in the distal lower extremities, autonomic dysfunction (associated with orthostatic hypotension and constipation), and mild cognitive difficulties (often executive dysfunction). See Table 2.

More than 160 individuals of Ashkenazi and non-Ashkenazi Jewish heritage have been reported [Ziemssen et al 2000, Klein et al 2004, Mochel et al 2012, Hellmann et al 2015, Schiffmann et al 2018].

Table 2. Select Features of Classic *GBE1* Adult Polyglucosan Body Disease

Feature		% of Persons w/Feature
Upper motor neuron involvement	Neurogenic bladder	100%
	Spasticity	93%
Lower motor neuron involvement	Weakness	100%
	Sensory loss in distal lower extremities	94%
Autonomic dysfunction	Orthostatic hypotension	Unknown
	Constipation	
Cognitive decline / Dementia		47%

Based on Mochel et al [2012] and Hellmann et al [2015]

Classic *GBE1*-APBD

Neurogenic bladder. Urinary incontinence is often the first sign. As it progresses, appropriate management is required to prevent recurrent urinary tract infections and other complications.

Gait difficulties. Age of onset and severity vary among affected individuals; most individuals eventually require gait aids and possibly a wheelchair.

Sensory loss in the distal lower extremities is typically mild but can be severe enough to lead to painless foot injuries.

Autonomic dysfunction, identified by orthostatic intolerance, has been occasionally observed in affected individuals.

Mild cognitive difficulty (e.g., executive dysfunction) varies in severity and progression, with many affected individuals having mild involvement and some not having any cognitive involvement at all. Cognitive difficulties have not been well studied to date.

Life expectancy for *GBE1*-APBD, while not formally studied, is likely shortened.

Atypical *GBE1*-APBD

In their review of 50 individuals with *GBE1*-APBD from four reference centers, Mochel et al [2012] identified three individuals of non-Ashkenazi heritage who had atypical manifestations: one with Alzheimer disease-like dementia and axonal neuropathy, and two with subacute manifestations including a stroke-like episode in one and diaphragmatic failure in another.

An "intermediate form" of 1,4-alpha-glucan-branching enzyme (GBE) deficiency in two individuals of non-Ashkenazi Jewish heritage was associated with residual GBE activity – a history of infantile hepatomegaly and increased glycogen on liver biopsy that resolved spontaneously (in one individual) and a family history of severe infantile liver disease (in the other individual), and acute onset of neurologic manifestations in their 30s and 40s (about one decade earlier than typical APBD) followed by a relapsing-remitting course of acute neurologic deficits (mimicking multiple sclerosis) with subsequent neurologic impairment [Paradas et al 2014]. Brain MRI revealed non-progressive white matter lesions and spinocerebellar atrophy similar to typical APBD.

Other

Electrophysiologic testing

- Specialized autonomic testing (thermoregulatory sweat tests and autonomic reflex testing) shows sudomotor sweating abnormalities often with specific spinal cord level identified.
- Nerve conduction velocity and electromyogram reveal an axonal lumbosacral polyradiculoneuropathy.

Tissues with pathologic polyglucosan accumulation

- Sural nerve biopsy reveals characteristic polyglucosans within nerve sheaths. The extent and characteristics of the identified polyglucosans typically distinguish them from the rare polyglucosans found in normal older individuals [Xu et al 2019].
- Muscle. Diastase-resistant, periodic acid-Schiff (PAS)-positive material is characteristic.

Genotype-Phenotype Correlations

No clear correlation of clinical severity and *GBE1* pathogenic variants is known.

Prevalence

More than 160 individuals with *GBE1*-APBD of Ashkenazi Jewish heritage and non-Ashkenazi Jewish heritage (i.e., of Italian and German descent) have been reported in various studies [Ziemssen et al 2000, Klein et al 2004, Hussain et al 2012, Mochel et al 2012, Hellmann et al 2015, Schiffmann et al 2018]. Due to previous misdiagnosis, this is probably an underestimate.

The carrier frequency for *GBE1*-APBD is relatively high (1:83 deduced from testing 2,776 individuals self-reported to be 100% Ashkenazi Jewish [R Kornreich, unpublished data]) and, therefore, its prevalence is probably underestimated.

Genetically Related (Allelic) Disorders

The only other disorder known to be associated with biallelic pathogenic variants in *GBE1* is glycogen storage disease type IV (GSD IV). In GSD IV:

- GBE enzyme activity is typically undetectable or minimally detectable;
- Multiple homozygous or compound heterozygous *GBE1* pathogenic variants have been identified.

The phenotype associated with GSD IV spans a spectrum that includes the following forms (subtypes) based on age of presentation, clinical manifestations, and severity:

- **Fatal perinatal neuromuscular subtype.** Decreased fetal movements, polyhydramnios, and fetal hydrops that may be detected prenatally; arthrogryposis, severe hypotonia, muscle atrophy at birth, early neonatal death
- **Congenital neuromuscular subtype.** Profound neonatal hypotonia at birth, respiratory failure, dilated cardiomyopathy, early infantile death
- **Classic (progressive) hepatic subtype.** Failure to thrive; hepatomegaly; liver dysfunction; progressive liver cirrhosis with portal hypertension, ascites, and esophageal varices; hypotonia; and cardiomyopathy. Death typically by age five years from liver failure
- **Non-progressive hepatic subtype.** Liver dysfunction, myopathy, and hypotonia in childhood
- **Childhood neuromuscular subtype.** Chronic, progressive myopathy, with dilated cardiomyopathy in some

Differential Diagnosis

Delay in diagnosis of *GBE1* adult polyglucosan body disease (*GBE1*-APBD) is common because multiple sclerosis and primary urologic dysfunction are most commonly considered first.

Other disorders that may present similarly to *GBE1*-APBD include amyotrophic lateral sclerosis, cerebral small vessel disease (e.g., CADASIL, *HTRA1* disorder, and *COL4A1* and *COL4A2*-related small vessel disease), and peripheral neuropathies (e.g., Charcot-Marie-Tooth hereditary neuropathy) [Hellmann et al 2015]. These disorders can be excluded based on clinical findings because none exhibits the combination of pyramidal spastic paraparesis and peripheral neuropathy seen in nearly all individuals with *GBE1*-APBD.

Polyglucosan bodies. In adult polyglucosan body disease (*GBE1*-APBD), the polyglucosan bodies consist of periodic acid-Schiff (PAS)-positive material with diastase-resistant glucose polymers and are seen in the central and peripheral nervous system. In early infantile-onset glycogen storage disease type IV (see Genetically Related Disorders), polyglucosan bodies most commonly accumulate in the liver, heart, muscle, brain, spinal cord, peripheral nerve, and skin.

Other genes associated with polyglucosans are summarized in Table 3.

Table 3. Other Genes Associated with Accumulation of Polyglucosan Bodies

Gene(s)	Disorder	MOI
EPM2A *NHLRC1*	Progressive myoclonus epilepsy, Lafora type	AR

Table 3. continued from previous page.

Gene(s)	Disorder	MOI
GYG1 [1]	Polyglucosan body myopathy type 2 (OMIM 616199)	AR
	Glycogen storage disease type XV (OMIM 613507)	AR
PFKM	Glycogen storage disease type VII (OMIM 232800)	AR
PRKAG2	Glycogen storage disease of the heart, lethal congenital (OMIM 261740)	AD
RBCK1	Polyglucosan body myopathy 1 w/or w/o immunodeficiency (OMIM 615895)	AR

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
Based on Cenacchi et al [2019]
2. Tasca et al [2016]

Polyglucosan bodies also occur in double athetosis (Bielschowsky bodies) and normal older persons (corpora amylacea).

White matter changes on MRI. In individuals with *GBE1*-APBD, MRI shows increased T_2*-weighted signal in the periventricular white matter and possibly the brain stem, which may appear similar to that seen in multiple sclerosis; however, the images in *GBE1*-APBD typically do not enhance [Paradas et al 2014].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *GBE1* adult polyglucosan body disease (*GBE1*-APBD), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *GBE1* Adult Polyglucosan Body Disease

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic exam	• Obtain history for stroke-like episodes. • Assess for UMN (spasticity) & LMN involvement (weakness & sensory loss). • Brain & spine MRI (if not obtained at time of diagnosis) to exclude other causes of gait spasticity & neurogenic bladder
Musculoskeletal	Orthopedics / physical medicine & rehab / PT eval	To incl assessment of: • Muscle tone; joint range of motion; posture; mobility; strength, coordination & endurance; pain; bedsores • Need for adaptive devices • Footwear needs • PT needs
	OT eval	To assess: • Small motor function (hands, feet, face, fingers, toes) • ADL
Bladder function	History of spastic bladder symptoms: urgency, frequency, difficulty voiding	• Referral to urologist • Consider urodynamic eval & imaging of urinary tract & kidneys.
Orthostatic hypotension	History of postural dizziness & syncope	Test blood pressure for postural changes.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Constipation	History of constipation	Gastroenterology eval
Cognitive abilities	Assess cognitive function (executive function, language processing, visuospatial/ visuoconstructional skills, emotion regulation).	Referral to psychiatrist, psychologist, neuropsychologist if needed
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *GBE1*-APBD to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources; • Need for social work involvement for care-giver support; • Need for home nursing referral.	

ADL = activities of daily living; LMN = lower motor neuron; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Optimally, care is provided by a multidisciplinary team that includes specialists in physical medicine rehabilitation, urology, and behavioral neurology or psychology (i.e., behavioralists) (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *GBE1* Adult Polyglucosan Body Disease

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	Individualized PT program	• Stretching exercises to ↑ flexibility, ↓ spasticity, & maintain or ↑ joint range of motion & prevent joint contractures • Aerobic exercise to ↑ cardiovascular fitness & to maintain & ↑ muscle strength, coordination, & balance • Strengthening exercises to improve posture, walking, arm strength to improve use of mobility aids, ADL
	Reduction of spasticity	Massage, ultrasound, electrical stimulation, whirlpool
	Antispasmodic drugs	Baclofen, Botox®, dantrolene, tizanidine (used 1 at a time), esp early in disease course to ↓ cramps, make leg muscles less tight, & facilitate walking
Bladder function	Anticholinergic drugs; clean intermittent catheterization to prevent urosepsis	Consider indwelling bladder catheter depending on urologic findings.
	Treatment of recurrent UTIs	
Orthostatic hypotension	Per standard practice	
Constipation	Per standard practice	
Activities of daily living	PT	• Transfers (e.g., from bed to wheelchair, wheelchair to car) • Training on how to fall to ↓ risk of injury
	OT	• To accomplish tasks such as mobility, washing, dressing, eating, cooking, & grooming • To assist w/household modifications to meet special needs

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Cognitive decline / Dementia	Pharmacologic treatment	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, & psychosis)
	Psychotherapy / neuropsychological rehab	

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy; UTI = urinary tract infection

Surveillance

Table 6. Recommended Surveillance for Individuals with *GBE1* Adult Polyglucosan Body Disease

System/Concern	Evaluation	Frequency
Neurologic	• Neurologic assessment for progression of UMN & LMN signs • Monitor for development of new manifestations.	Per treating neurologist
Bladder function	Urology eval	Frequent
Orthostatic hypotension	Blood pressure testing for postural changes	Unknown
Constipation	Gastroenterology eval	Unknown
Activities of daily living	OT/PT eval	Per treating OT/PT
Cognitive decline	Per treating mental health clinicians	Per treating mental health clinicians
Genetic counseling	Update for new therapies, diagnostic methods, concerns of at-risk family members.	As needed

LMN = lower motor neuron; OT = occupational therapy/therapist; PT = physical therapy/therapist; UMN = upper motor neuron

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Clinical trials involve use of guaiacol [Kakhlon et al 2018] and triacyglycerol mimetic 5 (TGM5) [Alvarez et al 2017].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GBE1 adult polyglucosan body disease (*GBE1*-APBD) is inherited in an autosomal recessive manner.

Note: The fact that some individuals reported with *GBE1*-APBD had only a single pathogenic variant identified on molecular genetic testing led to the hypothesis that these individuals were "manifesting heterozygotes." A deep intronic pathogenic variant, not detected by routine sequence analysis, was identified as the second pathogenic variant in many of these individuals [Akman et al 2015]. Therefore, all data are consistent with autosomal recessive inheritance of *GBE1*-APBD.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *GBE1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *GBE1* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- If both parents are known to be heterozygous for a *GBE1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with *GBE1*-APBD are obligate heterozygotes (carriers) for a pathogenic variant in *GBE1*.

Other family members. Each sib of the proband's parents is at 50% risk of being a carrier of a *GBE1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GBE1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GBE1* pathogenic variants have been identified in the family, prenatal and preimplantation genetic testing for *GBE1*-APBD are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Adult Polyglucosan Body Disease Research Foundation (APBDRF)**
  8 West 37th Street
  Suite 901
  New York NY 10018
  Phone: 212-290-2546
  Fax: 212-643-0963
  Email: info@APBDRF.org
  www.apbdrf.org
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
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  Myelin Disorders Bioregistry Project

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. GBE1 Adult Polyglucosan Body Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GBE1	3p12.2	1,4-alpha-glucan-branching enzyme	GBE1 database	GBE1	GBE1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for GBE1 Adult Polyglucosan Body Disease (View All in OMIM)

263570	POLYGLUCOSAN BODY NEUROPATHY, ADULT FORM; APBN
607839	GLYCOGEN BRANCHING ENZYME; GBE1

Molecular Pathogenesis

The mammalian glucose storage molecule, glycogen, consists of approximately 55,000 units and yet is soluble. This solubility is achieved through branching. Glycogen synthase (GS) extends glucan chains and the 1,4-alpha-glucan-branching enzyme (GBE), encoded by *GBE1*, removes every six to seven units added and reattaches them on the side of a linear glucan chain. This converts the single chain to a two-pronged fork for GS to extend from each prong, and GBE to again branch, and so on, thus growing the molecule radially into a sphere, where all the hydrophobic chain surfaces are hidden within and the hydrophilic ends are exposed on the outside, rendering the overall massive globule soluble.

GBE deficiency thus leads to poorly branched and therefore insoluble glycogen (polyglucosans), which precipitates, aggregates, and accumulates into polyglucosan bodies (PB), which, being out of solution and aggregated, cannot be degraded by glycogen phosphorylase. The amassing aggregates in neurons lead over time to axon plugging, which causes the fatal progressive axonopathic disease *GBE1*-APBD.

Mechanism of disease causation. Loss of function

***GBE1*-specific laboratory technical considerations.** The second most common pathogenic variant, c.2053-5289_2053-5297delinsTGTTTTTTACATGACAGGT, is unlikely to be detected by typical exon-targeted and splice junction-targeted sequencing assays.

While GBE enzyme assay (in any tissue) is not a first-line diagnostic test for *GBE1*-APBD, frozen muscle tissue that includes sural nerve can be used in the evaluation of variants of uncertain significance.

Table 7. Notable *GBE1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000158.3 NP_000149.3	c.986A>C	p.Tyr329Ser	Founder variants in Ashkenazi Jewish population; most affected persons are homozygous for p.Tyr329Ser or compound heterozygous for both variants [Lossos et al 1998, Akman et al 2015]
NM_000158.3	c.2053-5289_2053-5297delins TGTTTTTTACATGACAGGT (IVS15+5289_5297delGTGTGG TGGinsTGTTTTTTACATGACAGGT)		

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

Dr Akman has a research laboratory at Columbia University Medical Center. He is working on the treatment of polyglucosan body diseases caused by GBE deficiency as well as RBCK1 deficiency. If you would like more information about his research or about the APBD Research Foundation, contact Dr Akman at hoa2101@cumc.columbia.edu.

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- 17 September 2020 (bp) Comprehensive update posted live
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