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Glycogen Storage Disease Type V

Synonyms: Glycogenosis Type V, GSDV, McArdle Disease, Muscle Glycogen Phosphorylase Deficiency, Myophosphorylase Deficiency, PYGM Deficiency

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Summary

Clinical characteristics

Glycogen storage disease type V (GSDV, McArdle disease) is a metabolic myopathy characterized by exercise intolerance manifested by rapid fatigue, myalgia, and cramps in exercising muscles. Symptoms are usually precipitated by isometric exercise or sustained aerobic exercise. Most individuals improve their exercise tolerance by exploiting the "second-wind" phenomenon with relief of myalgia and fatigue after a few minutes of rest. Age of onset is frequently in the first decade of life but can vary; however, diagnosis is typically delayed as myalgia and fatigability are dismissed/overlooked. Fixed muscle weakness occurs in approximately 25% of affected individuals, is more likely to involve proximal muscles, and is more common in individuals of advanced age. Approximately 50% of affected individuals have recurrent episodes of myoglobinuria that can – on occasion – eventually result in acute renal failure.

Diagnosis/testing

The diagnosis of GSDV is established in a proband with suggestive findings and by identification of biallelic *PYGM* (encoding glycogen phosphorylase, muscle form) pathogenic variants on molecular genetic testing or – if genetic test results are not diagnostic – by assay of muscle myophosphorylase enzyme activity.

Management

Treatment of manifestations: Although no cure for GSDV is available, affected individuals benefit from moderate-intensity aerobic training (e.g., walking or brisk walking, bicycling) to increase cardiorespiratory fitness and muscle oxidative capacity. Pre-exercise ingestion of sports drinks containing simple carbohydrates improves exercise tolerance and may protect against exercise-induced rhabdomyolysis.

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Surveillance: Annual routine physical examination and review of diet.

Agents/circumstances to avoid: To prevent occurrence of cramps and myoglobinuria, avoid intense isometric exercise and maximal aerobic exercise.

Evaluation of relatives at risk: When the family-specific *PYGM* pathogenic variants are known, early detection of GSDV in relatives at risk ensures proper management to prevent muscle injury leading to rhabdomyolysis and to improve long-term outcome, particularly by development of a healthy lifestyle (i.e., regular exercise such as brisk walking) in childhood.

Genetic counseling

GSDV is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. Heterozygotes are asymptomatic. Once the pathogenic variants in the family are known, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Glycogen storage disease type V **should be suspected** in individuals with the following supportive findings.

Clinical findings

- Childhood onset of exercise-induced muscle contractures and pain, especially during the first approximately ten minutes of exercise. Although symptoms are frequently noted in physical education classes or on the school playground, their significance is not usually recognized, and diagnosis is delayed until most affected individuals are older.
- Second-wind phenomenon, i.e., improvement in exercise-induced muscle cramps and/or pain after a brief rest period when exercise intensity is reduced, or after the first (~) ten minutes of continuous exercise at the same constant, moderate intensity (see **Other findings**, **Cycle and walking tests**).
- Episodes of rhabdomyolysis (which can result in myoglobinuria) triggered by persistent skeletal muscle activity despite symptoms (i.e., before getting into the second-wind phenomenon), intense exertion, anaerobic activity (e.g., sprinting to catch a bus), lifting heavy weights, isometric contraction (e.g., carrying weights), and sustained muscle contraction [Scalco et al 2015]
- Unusual clinical presentations such as difficulty with mastication, dysphagia, and oral motor function appear to be more common in younger individuals. Other rare presentations are spontaneous compartment syndrome [Triplet et al 2017] or acute contracture of posterior neck muscles (e.g., during dental procedures) [Scalco et al 2016].
- Some affected individuals have minimal symptoms (i.e., only during strenuous exercise) with essentially no limitations in activities of daily living [Pinós et al 2015].
- Physical activity habits may explain variability in phenotypic manifestations of GSDV: individuals who are physically active at work or during their leisure time are less affected [Lucia et al 2012].

Other findings

- **A wide range of high resting serum creatine kinase (CK) activity.** Mean values frequently exceed 1,000 IU/L (normal reference values: <200 IU/L).

- **Cycle and walking tests** are physiologic exertion tests used to detect the pathognomonic heart rate response of the second-wind phenomenon observed in all individuals with GSDV.

  The cycle test is positive when the first ~10 minutes of cycling elicits a marked increase in heart rate (>30-40 beats/min) at a moderate, constant load (~40 watts for most adults*) and frequent muscle symptoms (myalgia and contractures), followed by a decrease in both heart rate (from ~150 to ~120 beats/min) and muscle symptoms [Lucia et al 2012].

  * Corresponding to a heart rate of 60%-70% of the predicted maximum heart rate (i.e., 220 beats/min minus age in years)

  The walking test can be performed in less specialized clinical settings [Buckley et al 2014].

- **Forearm non-ischemic exercise test** detects low values of post-exercise plasma lactate-to-ammonia ratio in persons with GSDV, is easy to perform in clinical settings, and has high sensitivity and specificity [Hogrel et al 2015].

Establishing the Diagnosis

The diagnosis of glycogen storage disease type V is established in a proband with suggestive findings and biallelic *PYGM* pathogenic variants identified on molecular genetic testing (see Table 1) or – if genetic test results are not diagnostic – by assay of muscle myophosphorylase enzyme activity.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing or genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of glycogen storage disease type V is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of glycogen storage disease type V has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of glycogen storage disease type V, options can include **single-gene testing** or a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *PYGM* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications [García-Consuegra et al 2009]. Sequencing of *PYGM* cDNA of peripheral blood cells has proven useful in individuals with a gene variant of uncertain pathogenicity that has apparently synonymous effects [García-Consuegra et al 2016].

- **A metabolic myopathy or rhabdomyolysis multigene panel** that includes *PYGM* 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 [Olpin et al 2015, Santalla et al 2017]. 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of glycogen storage disease type V is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option [Walters et al 2018].

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.

Table 1. Molecular Genetic Testing Used in Glycogen Storage Disease Type V

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PYGM	Sequence analysis [3]	99% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. García-Consuegra et al [2016], Santalla et al [2017]
5. 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.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. A 1,094-bp deletion variant, c.1969+214_2177+369del, extends from intron 16 to intron 17 [García-Consuegra et al 2009].

A clinical utility card regarding genetic test usage for *PYGM* has been published [Taylor et al 2018].

Assay of myophosphorylase enzyme activity. Myophosphorylase E.C. 2.4.1.1 is the muscle isoenzyme of glycogen phosphorylase (GP). Qualitative histochemistry or quantitative biochemical analysis in a muscle biopsy or muscle homogenate is diagnostic. In persons with GSDV, residual activity of myophosphorylase is virtually undetectable.

Clinical Characteristics

Clinical Description

Glycogen storage disease type V (GSDV) is a metabolic myopathy with onset frequently in the first decade of life. Clinical heterogeneity exists; about 10% of all affected individuals have mild manifestations (e.g., fatigue or poor stamina without contractures) and remain virtually asymptomatic during daily activities of living [Santalla et al 2017], whereas a more severe, rapidly progressive form may manifest shortly after birth. In some individuals, progressive weakness manifests in the sixth or seventh decade of life. The fixed weakness that occurs in approximately 20% of affected individuals is more likely to involve proximal muscles and is more common in

individuals older than age 40 years [Santalla et al 2017]. Most affected individuals learn to adjust their daily activities and can lead relatively normal lives.

The usual presentation of GSDV is exercise intolerance (including contractures, stiffness, and/or weakness of the muscles in use), myalgia, and fatigue in the first few minutes of exercise. These symptoms are usually precipitated by isometric exercise (e.g., carrying weights) or sustained vigorous "aerobic" exercise (e.g., stair climbing, jogging), and typically are relieved by rest. Any skeletal muscle can be affected. Recurrent episodes of myoglobinuria as a consequence of such exercise are observed in about 50% of affected individuals [Santalla et al 2017].

Atypical presentations have been also described, such as difficulty with mastication, dysphagia, and oral motor function (which appear to be more common in younger individuals) [Kouwenberg et al 2018], spontaneous compartment syndrome [Mull et al 2015, Triplet et al 2017], and acute contracture of the posterior neck muscles [Scalco et al 2016].

While most affected individuals remember painful symptoms from early childhood, the disorder is rarely diagnosed before adulthood (i.e., usually after age 20 years, median age 33 years) [Santalla et al 2017, Scalco et al 2017]. Some people notice in middle age a worsening of their symptoms that may be accompanied by some muscle wasting. Presentation with exertional dyspnea has been described.

Most individuals learn to improve their exercise tolerance by exploiting the second-wind phenomenon, a unique feature of GSDV, which is relief of myalgia and rapid fatigue after a few minutes of rest. The metabolic events underlying the second wind are the increased supply of blood-borne glucose and free fatty acids as exercise progresses, leading to an increase in the rate of metabolism of these fuels inside working muscle fibers. The ability to develop a second wind is greatly increased in those who stay physically fit with regular aerobic exercise, such as walking.

In contrast, continuing to exercise in the presence of severe pain might result in muscle damage (rhabdomyolysis) and myoglobinuria. Myoglobinuria due to rhabdomyolysis following intense exercise occurs in approximately 50% of individuals; despite the risk of acute renal failure, very few develop it. While kidney failure is almost always reversible, emergency treatment is required [Lucia et al 2012]. It is noteworthy that a history of dark urine could help avoid misdiagnosis and complications of GSDV [Scalco et al 2016, Martinez-Thompson et al 2017].

Other presentations of GSDV:

- Severe paraspinal wasting and weakness [Witting et al 2014]
- Incidental finding of severe obstructive hypertrophic cardiomyopathy [Moustafa et al 2013]
- Acute renal failure in the absence of exertion
- HyperCKemia (asymptomatic elevations of serum CK activity) up to 17,000 IU/L in the infantile myopathy and preadolescents.

Pathophysiology. The two types of exercise:

- Aerobic exercise includes walking, gentle swimming, jogging, and cycling. During aerobic exercise, the fuel used by skeletal muscle depends on several factors including the following: type, intensity, and duration of exercise; physical condition; and dietary regimen. Because aerobic exercise favors the utilization of blood-borne substrates, such as fatty acids, it is better tolerated by individuals with GSDV and thus beneficial as a therapeutic regimen.
- "Anaerobic" exercise is intense and cannot be sustained (e.g., weight lifting or 100-meter dash). Normally, during anaerobic exercise, myophosphorylase converts glycogen to glucose, which enters the glycolytic pathway and produces ATP "anaerobically" (or with no need for oxygen).

The first few minutes of any exercise have an anaerobic component. Depending on intensity and duration of the exercise, muscle uses different fuel sources such as anaerobic glycolysis, blood glucose, muscle glycogen, and aerobic glycolysis, followed by fatty acid oxidation.

At rest the main energy source is blood free fatty acids. These molecules are oxidized in the mitochondrial beta-oxidation pathway to produce acetyl-CoA, which is further metabolized through the Krebs cycle and the mitochondrial respiratory chain resulting in ATP production.

Genotype-Phenotype Correlations

Several studies in European populations have not found an association between severity of clinical findings and *PYGM* genotype [Santalla et al 2017].

Prevalence

The prevalence of GSDV in the Dallas-Fort Worth, Texas, area was estimated at 1:100,000.

The Spanish McArdle Disease patient registry reported a minimum prevalence in Spain of nearly 1:170,000 [Lucia et al 2012, Santalla et al 2017].

Genetically Related (Allelic) Disorders

Late-onset limb-girdle myopathy, ptosis, and camptocormia (i.e., flexion of the torso during walking or standing caused by weakness of the spinal extensors; resolves in the supine position), with no history of exercise intolerance, was reported in two unrelated individuals over age 75 years, both of whom were homozygous for the same novel *PYGM* frameshift pathogenic variant [Chéraud et al 2018].

Differential Diagnosis

The differential diagnosis of glycogen storage disease type V (GSDV) includes mitochondrial myopathy (mitochondrial myopathy is genetically heterogeneous [see Mitochondrial Disorders Overview]) and the disorders associated with the genes listed in Table 2. Because most of the disorders in Table 2 have different forms (i.e., hepatic and muscle), information included in the table pertains to the myopathic forms that are usually manifest in children or adults. For the purposes of differential diagnosis, clinicians should be aware that the second-wind phenomenon is virtually pathognomonic for GSDV.

Table 2. Other Genes of Interest in the Differential Diagnosis of Glycogen Storage Disease Type V (GSDV)

Gene(s) [1]	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/GSDV	Distinguishing from GSDV
ACADVL	VLCAD deficiency	AR	• Exercise intolerance • Intermittent rhabdomyolysis	• Precipitants: prolonged exercise, fasting, cold, fever • Normal basal CK
CAV3	Isolated hyperCKemia (OMIM 123320) [2]	AD	Persistent hyperCKemia (4- to 17-fold higher than normal)	• No clinical findings of muscle disease • Normal lactate exercise testing
CPT2	Carnitine palmitoyl transferase II deficiency	AR	• Myoglobinuria • Cramps, premature fatigue	• Precipitants: after prolonged exercise, fasting, fever • Basal CK (inter-episodic) normal

Table 2. continued from previous page.

Gene(s) [1]	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/GSDV	Distinguishing from GSDV
HADHA *HADHB*	Mitochondrial trifunctional protein deficiency (See Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency.)	AR	Episodic myoglobinuria	Mild sensorimotor axonal peripheral neuropathy
LDHA	GSDXI [3] (OMIM 612933)	AR	Exertional myoglobinuria	• ↑ lactate & pyruvate on exercise testing • Uterine muscle may be stiff during pregnancy.
PFKM	GSDVII [4] (OMIM 232800)	AR	• Exercise intolerance cramps & myglobinuria • No ↑ of lactate on exercise test	• Compensated hemolysis • Hyperuricemia
PGAM2	GSDX [5] (OMIM 261670)	AR	• Myoglobinuria, intolerance for strenuous exercise • Basal serum CK ↑	
PGK1	Phosphoglycerate kinase 1 deficiency (OMIM 300653)	XL	• Muscle cramps w/exercise • Rhabdomyolysis	• Hemolytic anemia • CNS involvement
PHKA1 *PHKB* *PHKG2*	Phosphorylase kinase deficiency, muscle forms	XL AR	• Exercise intolerance • Myalgia, cramps • Myoglobinuria • Progressive muscle weakness	

AD = autosomal dominant; AR = autosomal recessive; CK = creatine kinase; CNS = central nervous system; DiffDx = differential diagnosis; GSD = glycogen storage disease; MOI = mode of inheritance; VLCAD = very long-chain acyl-CoA dehydrogenase; XL = X-linked

1. Genes are in alphabetic order.
2. Also referred to as "creatine phosphokinase, elevated serum"
3. Lactate dehydrogenase deficiency
4. Phosphofructokinase deficiency
5. Phosphoglycerate mutase deficiency

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with glycogen storage disease type V (GSDV), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Physical examination with emphasis on muscle strength/weakness
- Basal serum CK activity
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Currently, simple healthy lifestyle interventions (i.e., following a diet rich in complex carbohydrates and regular exercise practice), the most effective means of preventing and managing exercise intolerance in GSDV, require a proactive attitude of clinicians, exercise professionals, and patient advocates [Nogales-Gadea et al 2016].

The benefits of a professionally supervised exercise program are safety and ease of implementation. Patients with GSDV generally adapt well to regular exercise; training should be designed to ensure gradual progression of exercise intensity, especially in the more severely affected patients. For children, it is important to provide parents, caregivers, and educators (especially physical education teachers) with appropriate information to ensure their best possible management. Patients who commit to a supervised, gradual exercise program are able to improve their fitness levels almost as effectively as healthy individuals. Indeed, affected individuals may become virtually asymptomatic during activities of daily living. It should also be noted that physical activity in general has been associated with improvements in peak oxygen uptake (VO2peak, or "cardiorespiratory fitness" [CRF]), an important health indicator. For more details on exercise recommendations and pre-exercise nutrition schedules see Nogales-Gadea et al [2016].

A systematic review of physical training for GSDV published in the Cochrane Database found no randomized or quasi-randomized controlled trials of aerobic training in people with GSDV; however, three studies using small numbers of participants provided some evidence that aerobic training improves CRF without adverse events and called for larger controlled trials of aerobic training in patients with GSDV [Quinlivan et al 2011].

Historically, patients with GSDV have been advised to avoid resistance (strength) exercises and other forms of physical activity involving high mechanical loads such as prolonged isometric contraction. However, a recent study of seven adults (5 female) showed improved muscle strength and mass (clinically as well as objectively using dual-energy x-ray absorptiometry) following a four-month-long resistance training program (i.e., weight lifting with qualified instruction and supervision and a two-month detraining period [Santalla et al 2014]. Further evidence on the safety of this type of exercise was reported in two other patients [Pietrusz et al 2018].

Pharmacologic and Nutritional Treatments

A revised and updated systematic review in the Cochrane Database of nutritional and pharmacologic trials for GSDV [Quinlivan et al 2014 (updated from 2008)] indicate that high-dose oral ribose, fat-rich diet, glucagon, verapamil, vitamin B_6, high-protein diet, branched-chain amino acid supplementation, dantrolene sodium, high-dose creatine, intravenous gentamicin, ketogenic diet, and intralipid infusion treatments showed no benefit. Treatments that showed some benefit included oral sucrose, carbohydrate-rich diet, ramipril, and low-dose creatine.

The study concluded that: (1) consuming a sugary drink before planned strenuous exercise can improve performance but is not practical for day-to-day living; (2) a diet rich in complex carbohydrates may be superior to a diet rich in protein; however, because of the small number of participants, evidence was insufficiently strong to indicate a significant clinical benefit; (3) ramipril 2.5 mg orally daily showed some subjective improvement in participants with the DD-ACE polymorphism, which is thought to have a modulating effect on the condition; however, there was no improvement in objective measures of exercise performance; and (4) low-dose creatine supplementation demonstrated a statistically significant (albeit modest) benefit in the tolerance to ischemic exercise in a small number of individuals [Quinlivan et al 2014].

Details of interventions with pre-exercise nutrition and physical exercise recommendations are set forth in Nogales-Gadea et al [2016].

Because of the rarity of GSDV, multicenter collaboration and standardized assessment protocols are needed for future treatment trials.

Prevention of Primary Manifestations

See Treatment of Manifestations and Agents/Circumstances to Avoid.

Surveillance

Appropriate surveillance includes the following:

- Annual routine physical examination
- Annual review of diet

Agents/Circumstances to Avoid

Exercises that should be avoided in patients with GSDV [Lucia et al 2008, Quinlivan et al 2011, Lucia et al 2012] are the following:

- Static muscle contractions (e.g., handgrip exercises)
- Static muscle contractions or heavy loads on low muscle mass (e.g., weight lifting), unless performed under programmed supervision of clinicians and exercise/fitness specialists [Santalla et al 2014, Nogales-Gadea et al 2016]
- Dynamic exercises at a high-intensity level (e.g., competitive ball games)
- Exercises with a high involvement of eccentric (lengthening) muscle contractions (e.g., jumps)
- Very intense dynamic aerobic exercise (e.g., running, strenuous swimming, or cycling) except in very fit individuals who are also well trained for the specific activity

General anesthetics. Risk of acute muscle damage is reported with certain general anesthetics (usually muscle relaxants and inhaled anesthetics), although in practice, problems appear to be rare. Nonetheless, measures for preventing muscle ischemia and rhabdomyolysis should be taken in individuals with GSDV [Bollig 2013].

Evaluation of Relatives at Risk

It is appropriate to clarify the clinical/genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual as early diagnosis of GSDV may improve long-term outcome by heightening awareness of the need to avoid repetitive episodes of muscle damage that may lead to rhabdomyolysis and fixed weakness.

- Molecular genetic testing can be used for evaluation of relatives at risk if the *PYGM* pathogenic variants in the family are known.
- If the family-specific *PYGM* pathogenic variants are not known, a reliable and accurate diagnosis of GSDV could be reached following the criteria described in Diagnosis.

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

Pregnancy Management

GSDV does not appear to adversely affect pregnancy or childbirth [Lucia et al 2012, Stopp et al 2018].

Therapies Under Investigation

Preclinical studies (animal models) have shown that sodium valproate, a histone deacetylase inhibitor, (1) increases GP expression in muscle fibers from McArdle sheep [Howell et al 2015] and (2) induces the expression of the brain isoenzyme, GP-BB, with a decrease of glycogen accumulation in primary skeletal muscle cultures derived from a McArdle knock-in mouse [de Luna et al 2015].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

Glycogen storage disease type V (GSDV) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *PYGM* pathogenic variant).
- Although some heterozygotes (carriers) may manifest mild exercise-related muscle symptoms, heterozygotes are not at risk of developing GSDV and are typically asymptomatic (see Carrier Detection).

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are typically asymptomatic (see Carrier Detection).

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

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

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *PYGM* pathogenic variants in the family.

Note: Although manifesting heterozygotes (i.e., carriers of only 1 *PYGM* pathogenic variant) who show some GSDV-like symptoms or signs were reported before genetic testing was available, recent evidence does not support those observations:

- In a study of 26 individuals – eight with GSDV, seven heterozygotes, and 11 controls – the heterozygotes and controls had identical values of exercise capacity indicators (maximal oxidative capacity and peak lactate response), suggesting that heterozygotes are not prone to developing symptoms of GSDV [Andersen et al 2006].
- In a more recent study of 81 relatives of individuals with GSDV (50 *PYGM* carriers and 31 non-carriers), 14% of carriers manifested exercise-related muscle symptoms (e.g., exacerbated myalgia or weakness) that were milder than those commonly reported in affected individuals. Furthermore, no carriers (whether symptomatic or not) showed either hallmark of GSDV: the second-wind phenomenon or a flat blood lactate response to maximal-intensity exercise [Núñez-Manchón et al 2018].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *PYGM* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Biochemical testing. Biochemical testing cannot be done on fetal tissue as myophosphorylase is expressed only in differentiated muscle cells.

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.

- **Asociación Española de Enfermos de Glucogenosis (AEEG)**
  Spain
  Email: aeeg@glucogenosis.org
  Glucogenosis tipo V o enfermedad de McArdle
- **Association for Glycogen Storage Disease**
  United Kingdom
  Email: gsd5@agsd.org.uk
  McArdle Disease (GSD5)
- **MedlinePlus**
  McArdle syndrome
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Muscular Dystrophy Association (MDA) - USA**

Phone: 833-275-6321
Email: ResourceCenter@mdausa.org
mda.org

- **EUROMAC**
  Spain
  www.euromacregistry.eu

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. Glycogen Storage Disease Type V: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PYGM	11q13.1	Glycogen phosphorylase, muscle form	PYGM database	PYGM	PYGM

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 Glycogen Storage Disease Type V (View All in OMIM)

232600	GLYCOGEN STORAGE DISEASE V; GSD5
608455	GLYCOGEN PHOSPHORYLASE, MUSCLE; PYGM

Molecular Pathogenesis

Genetic alterations in *PYGM* result in a lack or deficiency of muscle glycogen phosphorylase, which catalyzes the breakdown of glycogen into glucose-1-phosphate in this tissue. The enzyme exists as a homodimer containing two identical subunits; the dimers associate into a tetramer to form the enzymatically active phosphorylase. Therefore, some pathogenic variants may affect tetramer formation.

Mechanism of disease causation. Loss of function; skeletal muscle shows lack or deficiency of glycogen phosphorylase.

Table 3. Notable Recurrent *PYGM* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Recurrent Variants
NM_005609.2 NP_005600.1	c.148C>T	p.Arg50Ter	See footnote 1.
	c.255C>A	p.Tyr85Ter	Individuals of Central European descent
	c.613G>A	p.Gly205Ser	10% of alleles in US & 9% in Spain; never in Japanese [1, 2]
	c.2128_2130delTTC	p.Phe710del	The most common *PYGM* variant in Japan [1]
	c.2392T>C	p.Trp798Arg	Found in 10% of Spanish individuals w/GSDV [2]

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.
See the review by Nogales-Gadea et al [2015] for additional details.
1. The variant p.Arg50Ter (previously p.Arg49Ter) is the most common pathogenic variant in individuals of European and US descent. Frequency (among all variants) of p.Arg50Ter observed by population: 81% (English), 63% (North American), 56% (German), 56% (French), 55% (Spanish); p.Arg50Ter has never been found in individuals of Japanese descent [Nogales-Gadea et al 2015 and references therein].
2. Santalla et al [2017]

Chapter Notes

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Revision History

- 20 June 2019 (bp) Comprehensive update posted live
- 26 June 2014 (me) Comprehensive update posted live
- 12 May 2009 (me) Comprehensive update posted live
- 8 May 2006 (cd) Revision: sequence analysis of *PYGM* clinically available
- 19 April 2006 (me) Review posted live
- 26 August 2005 (ja) Original submission

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