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Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Glycogen Storage Disease Type V

[*Glycogenosis Type V, McArdle Disease, Muscle Glycogen Phosphorylase Deficiency, Myophosphorylase Deficiency, GSDV*]

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Initial Posting: April 19, 2006.
Last Revision: May 8, 2006.

Summary

Disease 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, and, in about 50% of individuals, episodes of myoglobinuria that can result in acute renal failure. Symptoms usually are precipitated by isometric exercise and sustained aerobic exercise. Most individuals learn to improve their exercise tolerance exploiting the "second wind" phenomenon with relief of myalgia and fatigue after a few minutes of rest. Onset of GSDV typically occurs in the second to third decade of life. Individuals may present with exercise intolerance; acute renal failure; hyper-CK-emia; or clumsiness, lethargy, slow movement, or laziness in pre-adolescents. Clinical variability exists; some individuals have mild symptoms manifesting as tiredness or poor stamina without cramps. In some individuals, progressive weakness becomes manifest in the sixth or seventh decade of life. The severe rapidly progressive form manifests shortly after birth. Fixed weakness occurs in about one third of affected individuals, is more likely to involve proximal muscles, and is more common in individuals of advanced age.

Diagnosis/testing. GSDV is diagnosed by clinical findings and supportive laboratory data (i.e., an increased resting basal serum creatine kinase [CK] activity and a flat response of lactate to the forearm ischemic test) or the cycle test, a specific, sensitive, and simple diagnostic test, which takes advantage of the pathognomonic heart rate response related to the second wind phenomenon. The diagnosis is confirmed either by assay of myophosphorylase enzyme activity or by molecular genetic testing. *PYGM*, the gene encoding myophosphorylase, is the only gene associated with GSDV. Targeted mutation analysis of the most common mutations, R49X and G204S, and sequence analysis of the entire coding region are available on a clinical basis.

Management. No specific treatment for GSDV is recommended. Individuals with GSDV benefit from aerobic training to increase circulatory capacity and increase delivery of blood-borne fuels. Creatine monohydrate may improve symptoms and increase capacity for ischemic, isometric exercise. Ingestion of sucrose improves exercise tolerance and may protect against exercise-induced rhabdomyolysis. Surveillance includes annual routine physical examination and review of diet. To prevent cramps and myoglobinuria, individuals should avoid intense isometric exercise and maximal aerobic exercise. General anesthesia may cause acute muscle damage. Early detection of GSDV in relatives at risk ensures proper management to prevent muscle injury leading to rhabdomyolysis and to improve long-term outcome.

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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Heterozygotes are generally asymptomatic. Carrier testing for at-risk family members and prenatal diagnosis for pregnancies at increased risk are available on a clinical basis if the mutations have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Glycogen storage disease type V [McArdle 1951] is suspected in individuals with exercise-induced muscle cramps and pain, episodes of myoglobinuria, and supportive laboratory data (i.e., an increased resting basal serum creatine kinase [CK] activity and a flat response of lactate to the forearm ischemic test) [DiMauro & Tsujino 1995]. The diagnosis is confirmed either by molecular genetic testing or assay of myophosphorylase enzyme activity.

Testing

Serum creatine kinase (CK) activity. A wide range of persistently elevated activities is seen, with values usually around 1,000 U/L. (Normal reference values: <170 IU/L.)

Lactate forearm test (LFT)

- **The non-ischemic lactate forearm test,** the preferred lactate forearm test, relies on sampling plasma lactate concentration and plasma ammonia concentration at baseline and within the first two minutes following exercise consisting of repeated maximal one-second handgrips every other second for one minute (30 contractions). Diagnostic changes in plasma lactate concentration and plasma ammonia concentration always occur within the first two minutes after exercise [Kazemi-Esfarjani et al 2002].

  Note: Persons with glycogenoses have exaggerated responses of plasma ammonia concentration to exercise; therefore, measuring plasma ammonia concentration is as informative as measuring plasma concentration of lactate.

  In normal controls, lactate levels increase five to six times above basal values.

  In GSDV:

  - The plasma lactate concentration does not increase (the so-called "flat lactate curve").
  - Post-exercise lactate-to-ammonia peak ratios are clearly decreased.

- **The ischemic lactate forearm test** was used until recently to assess the response of plasma lactate concentration to exercise in individuals with GSDV. Drawbacks to the lactate forearm ischemic test include:
  - False positive results in weak or unmotivated persons
  - Lack of specificity for GSDV (i.e., the test is positive with any block in glycogenolysis or glycolysis)
  - Pain and risk of local muscle damage resulting in myoglobinuria or compartment syndrome

The non-ischemic lactate forearm test [Kazemi-Esfarjani et al 2002] has the same diagnostic power as the ischemic lactate forearm test, but eliminates the cramps, pain, and potential muscle injury produced by the ischemic test.

Cycle test. The cycle test, a physiologic test in which only heart rate needs to be monitored, takes advantage of the pathognomonic heart rate response related to the second wind phenomenon, which is present in all individuals with GSDV. A controlled case study [Vissing & Haller 2003a] indicates that cycling at a moderate, constant workload provides a specific, sensitive, and simple diagnostic test for GSDV.

Myophosphorylase enzyme activity. Myophosphorylase E.C. 2.4.1.1 is the muscle isoenzyme of glycogen phosphorylase [Browner & Fletterick 1992]. Qualitative histochemistry or quantitative biochemical analysis in a muscle biopsy or muscle homogenate is diagnostic. The residual activity of myophosphorylase is virtually undetectable. For laboratories offering biochemical testing, see

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Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *PYGM*, encoding myophosphorylase, is the only gene associated with GSDV.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier detection
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis**

  R49X is the most common mutation among individuals of European and US descent. It is a nonsense mutation at codon 49 in exon 1 [Bartram et al 1993, Tsujino et al 1993, El-Schahawi et al 1996, Andreu et al 1998, Martin et al 2001]. R49X has never been found in individuals of Japanese descent.

G204S is the second most common mutation, accounting for about nine percent of mutant alleles in various European and US populations.

- **Sequence analysis.** Sequencing of the entire coding region of the *PYGM* gene is clinically available [Kubisch et al 1998].

Ethnic background must be taken into account when molecular genetic testing is performed because of the presence of relatively common mutations in specific populations (Table 1).

Table 1. *PYGM* Mutations Other than R49X and G204S with Relatively High Frequency in Specific Populations

Population	Mutation	Frequency
Japanese [1]	708/709del	64%
Spanish [2]	W797R	14%
Central European [3]	Y84X	25%

1. Tsujino et al 1994
2. Fernandez et al 2000, Rubio et al 2000, Martin et al 2001
3. Deschauer et al 2003, Martin et al 2004

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Glycogen Storage Disease Type V

Test Methods	Mutations Detected	Percent of Mutant Alleles [1]	Mutation Detection Rate	Test Availability
Targeted mutation analysis [2]	R49X	32-64%	NA	Clinical Testing
	G204S	7-10%		
Sequence analysis	*PYGM* sequence variants	NA	Unknown	

NA = Not applicable

1. Percentages taken from Bartram et al 1993, Tsujino et al 1993, El-Schahawi et al 1996, Andreu et al 1998, Martin et al 2001
2. Although K542T is included in some panels, it is not commonly seen in GSDV.

Testing Strategy for a Proband

1 Clinical description of the type of exercise that precipitates the symptoms and a lactate forearm non-ischemic test.

2 If clinical findings and a LFT suggest a defect in muscle glycolysis or in glycogen metabolism, testing for the more common *PYGM* mutations (R49X and G204S) is recommended. If neither or only one mutation is identified, sequence analysis of the entire coding region can be considered. Molecular genetic testing provides a non-invasive and specific diagnosis [El-Schahawi et al 1996, Martin et al 2001].

3 If molecular genetic testing is not available or does not show homozygosity or compound heterozygosity for the common *PYGM* alleles, myophosphorylase enzyme activity should be analyzed histochemically and/or measured biochemically in muscle homogenates.

Genetically Related (Allelic) Disorders

An extremely rare infantile myopathy has been associated with the common R49X mutation in *PYGM* [DiMauro & Hartlage 1978, Milstein et al 1989]

Clinical Description

Natural History

Glycogen storage disease type V is a metabolic myopathy with onset typically in the second to third decade of life. Clinical heterogeneity exists; some individuals have mild symptoms manifesting as tiredness or poor stamina without cramps. In some individuals, progressive weakness becomes manifest in the sixth or seventh decade of life [Wolfe et al 2000]. In contrast, the severe rapidly progressive form manifests shortly after birth. Fixed weakness occurs in about one third of affected individuals, is more likely to involve proximal muscles, and is more common in individuals of advanced age.

Affected individuals have exercise intolerance manifested by rapid fatigue, myalgia, and cramps in exercising muscles, and nearly 50% of them experience recurrent myoglobinuria. Brief efforts involving isometric contraction and less intense but sustained dynamic exercise are most likely to cause symptoms. Most individuals learn to adjust their daily activities and can lead relatively normal lives [DiMauro & Tsujino 1995].

The usual presentation of individuals with GSDV is exercise intolerance, including stiffness or weakness of the muscles being used, myalgia, and fatigue in the first few minutes of exercise. These symptoms typically are relieved by rest. They usually are precipitated by isometric exercise (e.g., weight lifting) and sustained aerobic exercise (e.g., stair-climbing and jogging). Any skeletal muscle can be affected. Many individuals remember painful symptoms from early childhood but the disorder is rarely diagnosed before adulthood. Some people notice a worsening of their symptoms in middle age and this may be accompanied by some muscle wasting. Presentation with exertional dyspnea has been described [Voduc et al 2004].

Most individuals learn to improve their exercise tolerance exploiting the "second wind" phenomenon, a unique feature of GSDV [Braakhekke et al 1986], that 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 glucose and free fatty acids produced from extramuscular sources as exercise progresses, leading to a switch in metabolic pathways from endogenous glycolysis to oxidative phosphorylation of blood-borne fatty acids [Haller & Vissing 2002]. The ability to develop a second wind is greatly increased in those who keep physically fit through aerobic exercise, such as walking. In contrast, sustained or strenuous exercise, such as weight lifting or sprinting, carries a high risk of muscle damage. Continuing to exercise in the presence of severe pain also results in muscle damage (rhabdomyolysis) and myoglobinuria, with the attending risk of acute renal failure.

Myoglobinuria occurs in about 50% of individuals following intense exercise, and about one half of these individuals develop acute renal failure. Kidney failure is almost always reversible, but emergency treatment is required [DiMauro & Tsujino 1995].

Other presentations of GSDV include:

- Acute renal failure in the absence of an exertional component [Mittal et al 1995, Walker et al 2003, Sidhu & Thompson 2005].
- Hyper-CK-emia (asymptomatic elevations of serum creatine kinase). This has been reported in adolescents [Gospe et al 1998, Bruno et al 2000] and in one infant [Ito et al 2003].
- Clumsiness, lethargy, slow movement, or laziness observed in eight pre-adolescents [Roubertie et al 1998].

Pathophysiology. The two types of exercise are:

- **Aerobic exercise** including walking, gentle swimming, jogging, and cycling. During aerobic exercise, the fuel used by skeletal muscle depends on several factors, including 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, but cannot be sustained (e.g., weight lifting or 100-meter dash). Normally, during anaerobic exercise, myophosphorylase converts glyogen to glucose that enters the glycolytic pathway and produces ATP anaerobically.

The first few minutes of any exercise are usually anaerobic. 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 [DiMauro & Tsujino 1995].

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

One study in individuals of Spanish descent did not observe any apparent correlation between severity of clinical findings and genotype [Martin et al 2001].

One study showed that an angiotensin converter enzyme (ACE) insertion/deletion polymorphism might play a significant role as a phenotype modulator in individuals with GSDV [Martinuzzi et al 2003].

Prevalence

The prevalence of GSDV in the Dallas-Fort Worth, Texas, area was estimated to be about one in 100,000 [Haller 2000].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

- Mitochondrial myopathy (See Mitochondrial Disorders Overview.)
- Myodenylate deaminase
- Carnitine palmitoyl transferase II deficiency
- Phosphoglycerate kinase deficiency
- Phosphoglycerate mutase deficiency
- Phosphofructokinase deficiency
- Lactate dehydrogenase deficiency
- Phosphorylase b kinase deficiency
- Idiopathic hyper-CK-emia
- Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
- Mitochondrial trifunctional protein (MTP) deficiency

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Physical examination with emphasis on muscle strength/weakness
- Serum CK concentration

Treatment of Manifestations

Aerobic training (on a regular diet). In some individuals, improvement in exercise and circulatory capacity has been reported, probably caused by the increased circulatory capacity, which facilitates delivery of blood-borne fuels [Haller 2000].

Creatine monohydrate in a placebo-controlled crossover trial in nine individuals improved symptoms and increased their capacity for ischemic, isometric forearm exercise [Vorgerd et al 2000]. This positive effect did not result from increased levels of phosphocreatine in muscle. Rather, creatine may have a quenching effect on the potassium-mediated changes in membrane excitability. A subsequent clinical trial with high doses of creatine monohydrate in nineteen individuals lowered exercise intolerance [Vorgerd et al 2002]. The indication for symptomatic therapy with creatine monohydrate needs to be strengthened.

Ingestion of sucrose before exercise. In a single-blind, randomized, placebo-controlled crossover study in 12 individuals with GSDV, ingestion of sucrose markedly improved exercise tolerance [Vissing & Haller 2003b]. The treatment takes effect during the time when muscle injury commonly develops in GSDV. In addition to increasing exercise capacity and sense of well-being, the treatment may protect against exercise-induced rhabdomyolysis. Ingestion of sucrose before exercise combined with an aerobic conditioning program is reasonable [Amato 2003].

Three daily habits recommended by Haller (2000) to improve the quality of life:

- Avoid intense isometric exercise and maximal aerobic exercise, which would trigger cramps and, potentially, myoglobinuria.
- Avoid a totally sedentary life, which will induce deconditioning.
- Engage in regular, moderate aerobic exercise, which improves circulatory capacity and increases delivery of blood-borne fuels, a sort of permanent "second wind" (i.e., a decrease in heart rate and perceived exertion during exercise) effect [Ollivier et al 2005].

A systematic review of pharmacological and nutritional treatments for GSDV was published in the Cochrane Database [Quinlivan & Beynon 2004]. The authors' conclusions:

- It is not yet possible to recommend any specific treatment for GSDV.
- Low-dose creatine supplementation demonstrated a statistically significant benefit, albeit modest, in ischemic exercise in a small number of individuals.
- Ingestion of oral sucrose immediately prior to exercise reduces perceived ratings of exertion and heart rate and improves exercise tolerance. This treatment does not influence sustained or unexpected exercise and may cause significant weight gain.
- Because of the rarity of GSDV, multicenter collaboration and standardized assessment protocols are needed for future treatment trials.

Surveillance

- Annual routine physical examination

- Annual review of diet

Agents/Circumstances to Avoid

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. One report showed hyperthermia, pulmonary edema, and rhabdomyolysis [Lobato et al 1999]; however, GSDV does not seem to cause severe perioperative problems in routine anesthetic care. In this regard, measures for preventing muscle ischemia and rhabdomyolysis should be taken in individuals with GSDV [Bollig et al 2005].

Testing of Relatives at Risk

Early detection of GSDV in relatives at risk helps them prevent muscle injury leading to rhabdomyolysis. Because repetitive episodes of muscle damage may lead to fixed weakness, early diagnosis and proper management may improve long-term outcome.

Therapies Under Investigation

Gene therapy. An adenoviral recombinant containing the full-length human myophosphorylase cDNA was efficiently transduced into phosphorylase-deficient sheep and human myoblasts, where it restored enzyme activity [Pari et al 1999].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Vitamin B6 has been used because the overall body stores of piridoxal phosphate are depleted in GSDV. A beneficial effect has been documented in one individual, but this requires confirmation [Phoenix et al 1998].

Branched-chain amino acids (BCA). Administration of BCA as alternative fuels to glycogen to six individuals worsened bicycle exercise capacity, possibly because of the FFA-lowering effect of the amino acids [MacLean et al 1998].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are generally asymptomatic. However, manifesting carriers for some mutations have been described [Manfredi et al 1993].

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are generally asymptomatic.

Offspring of a proband. The offspring of an individual with GSDV are obligate heterozygotes (carriers) for a disease-causing mutation in the *PYGM* gene.

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

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

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 testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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

Requests for prenatal testing for conditions such as GSDV are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Glycogen Storage Disease Type V

Gene Symbol	Chromosomal Locus	Protein Name
PYGM	11q13	Glycogen phosphorylase, muscle form

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Glycogen Storage Disease Type V

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

Table C. Genomic Databases for Glycogen Storage Disease Type V

Gene Symbol	Entrez Gene	HGMD
PYGM	5837 (MIM No. 608455)	PYGM

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

The muscle glycogen phosphorylase (*PYGM*, glycogen phosphorylase, α-1,4-glucan orthophosphate glycosyltransferase, EC 2.4.1.1.) initiates glycogen breakdown by removing α-1,4-glucosyl residues phosphorylytically from the outer branches of glycogen with liberation of glucose-1-phosphate. The enzyme exists as a homodimer containing two identical subunits of 97,000 daltons each. The dimers associate into a tetramer to form the enzymatically active phosphorylase A.

Normal allelic variants: *PYGM* spans 14 kb containing 20 exons. Five single nucleotide polymorphisms in the coding region have been annotated (see Genomic Database Tables, GeneCards). Three non-synonymous (N188K, R414G, and S430L) and two synonymous (P498P and G455G) changes have been identified. Exonic polymorphisms should be tested by methods based on RNA instead of DNA because these mutations can be the underlying cause of splicing abnormalities [Fernandez-Cadenas et al 2003].

Pathologic allelic variants: A so-called "common" mutation occurs in exon one of *PYGM* at amino acid position 49, resulting in a premature stop codon. This mutation was identified in about 55% of all mutant alleles [Martin et al 2001].

G204S is the second most frequent mutation in various European and USA populations, representing about nine percent of mutant alleles.

Analysis of 54 individuals of Spanish origin showed that W797R was a frequent mutation in this population (14% of mutant alleles).

To date, 46 mutations causing *PYGM* deficiency have been identified. See Table 3 for classes of mutations observed.

Table 3. Classes of Mutations Observed in the *PYGM* Gene

Genetic Mechanism	Number of Mutations
Nucleotide substitutions (missense/nonsense)	34
Nucleotide substitutions (splicing)	3
Small deletions	8
Small indel mutations [1]	3
Total	**47**

1. Indel mutations (also called "indels") are the insertion and deletion of nucleotide sequences in the same region of a gene.

Silent exonic mutations ("silent polymorphisms") could have a potential pathogenic role as disease-causing mutations [Cartegni et al 2002]. This mutation class is probably involved in the regulation of the splicing machinery [Fernandez-Cadenas et al 2003], i.e., resulting in the synthesis of different transcripts of the *PYGM* gene, some of which can presumably be degraded, resulting in absence of protein, while others are translated into proteins with molecular weights lower than normal myophosphorylase.

Normal gene product: The size of monomeric *PYGM* is 841 amino acids in human skeletal muscle. *PYGM* protein has a molecular weight of 97 kd.

Abnormal gene product: Mutations in *PYGM* reduce or abolish myophosphorylase enzyme activity in muscle [Tsujino et al 1993, DiMauro et al 2002]. Missense mutations may affect contact dimer pairs, which are involved in the propagation of allosteric effects of this regulatory protein. Mutations can also disrupt hydrogen bond interactions and affect substrate or effector/inhibitor binding sites. Mutations yielding premature stop codons predict truncated proteins, but may also produce deep effects at the transcriptional level (i.e., non-sense mediated decay, disruption of splicing machinery yielding aberrant transcript) [Martin et al 2001, Fernandez-Cadenas et al 2003].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Association for Glycogen Storage Disease
P.O. Box 896
Durant IA 52747
Phone: 563-785-6038
Email: maryc@agsdus.org
www.agsdus.org

Medline Plus
McArdle syndrome

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
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Phone: (+44) 0870 7700 326
Fax: (+44) 0870 7700 327
Email: steve@climb.org.uk
www.climb.org.uk

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Acknowledgments

Supported by grants from the Fondo de Investigacion Sanitaria (FIS PI040487, FIS PI040362, PI050579, and the Spanish Neurological Diseases Network (FIS C03/06)

Revision History

- 8 May 2006 (cd) Revision: sequence analysis of *PYGM* clinically available
- 19 April 2006 (me) Review posted to live Web site
- 26 August 2005 (ja) Original submission