



Facts About **Limb-Girdle Muscular Dystrophies**

MDA[®] Muscular
Dystrophy
Association
Fighting Muscle Disease

Dear Friends:

When I was 4 years old, my parents took me to a specialist to find out why I walked with an unusual waddle. They learned I had limb-girdle muscular dystrophy.

Like many of you, we were shocked and scared by this diagnosis. My parents wondered why I had this disease; we had no history of it in our family. But, as this booklet explains, LGMD is caused by any of several rare genetic defects that people may not even know they have. That means it wasn't caused by anything you or your parents did, and you didn't catch it from anyone.

My family had to learn a lot about muscular dystrophy and make some major adjustments, both physical and psychological. Our world came to include doctor visits, leg braces, physical therapy and lots of questions. But gradually, muscular dystrophy just became a part of our lives, and we coped with it by learning all we could. Thanks to my determined parents, my devoted sister and the help of the Muscular Dystrophy Association, I had a wonderful childhood.

I graduated from college, and I'm now working in L.A. in the television industry. I use a wheelchair or scooter part time to help me when I work, travel and have fun with my friends.

I hope you can tell from my story that having limb-girdle muscular dystrophy doesn't mean the end of your choices or your dreams. It isn't easy to live with muscles that grow weaker over time, but you can have a very rewarding life with this condition.

Not everyone with LGMD has the same experience, but most of those I've met have busy, fulfilling lives like mine. I know of a writer, a doctor, an air traffic controller, some teachers, school and college

administrators, a real estate professional, a travel agency operator — all with limb-girdle MD. Many of these bright, active, independent people are married, and some have children — and grandchildren.

Those of us with LGMD have a lot of support today. People with disabilities have more opportunities than ever before to develop and use their abilities. Federal law guarantees us a public education, equal employment opportunity and access to public places. Computers and technology help me and other people with muscular dystrophy to move around, write, work and drive.

By far, my greatest ally in living with LGMD is MDA; I'm sure my parents would say the same thing. Be sure to read "MDA Is Here to Help You" on page 10! The Association is also the world leader in research on neuromuscular diseases, and its scientists have made many exciting discoveries about LGMD in the years since my diagnosis. We all pray for the day when no one has to have a neuromuscular disease.

This booklet will give you the basic facts about LGMD, and MDA will help you answer all your questions as they arise. As you face the challenges ahead, please remember two important things about having LGMD: First, MDA is making rapid progress toward better treatments and a cure. Second, you're not alone.

*Mandy
VanBenthuisen*

Mandy Van Benthuisen
Los Angeles



Mandy Van Benthuisen

What Is Limb-Girdle Muscular Dystrophy?

Limb-girdle muscular dystrophy (LGMD) isn't really one disease. It's a group of disorders affecting voluntary muscles, mainly those around the hips and shoulders — the pelvic and shoulder girdles, also known as the limb girdles.

You also may hear the term *proximal* used to describe the muscles that are most affected in LGMD. The proximal muscles are those closest to the center of the body; distal muscles are farther away from the center (for example, in the hands and feet). The distal muscles are affected late in LGMD, if at all.

Over time (usually many years), the person with LGMD loses muscle bulk and strength. Eventually, he may need a power wheelchair or scooter, especially for long distances.

LGMD can begin in childhood, adolescence, young adulthood or even later. Both genders are affected equally. When limb-girdle muscular dystrophy begins in childhood, some physicians say, the progression is usually faster and the disease more disabling. When the disorder begins in adolescence or adulthood, they say, it's generally not as severe and progresses more slowly.

What are the forms of limb-girdle muscular dystrophy?

There are at least 19 forms of LGMD, and they're classified by the genetic flaws that appear to cause them (see "Known Forms of Limb-Girdle Muscular Dystrophy, page 7). As of 2007, 15 specific genes that lead to production of muscle proteins have been implicated as definite causes of LGMD when they're flawed. MDA research was behind much of the work that identified these LGMD genes.

Genes, located on chromosomes in each cell in the body, are the codes, or recipes, for production of the body's various proteins. The genes associated with LGMD normally make proteins necessary for muscle function.

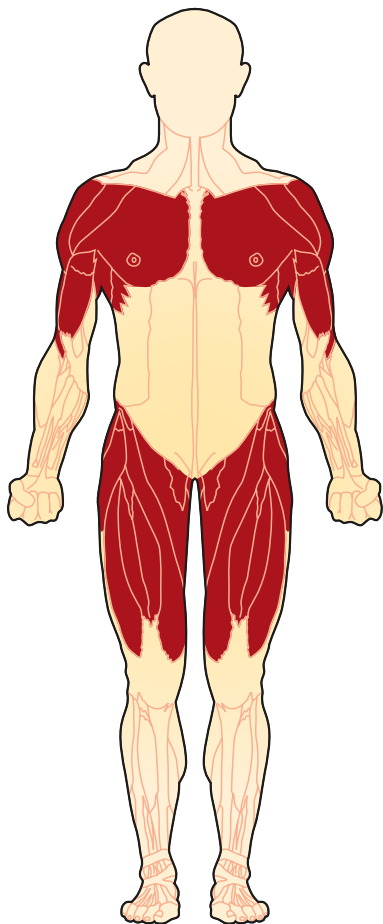
When protein problems arise because one of these genes is faulty, fibers in the muscles don't work properly. Gradually, the muscles become weak enough that people experience the symptoms of limb-girdle muscular dystrophy. Because LGMD is *progressive*, the muscles continue to get weaker throughout the person's lifetime.

Six of the genes that, when flawed, cause LGMD lead to production of proteins that are normally located in the muscle cell *membrane*. (The membrane is a thin sheath that surrounds each muscle cell, helping to protect it from injury during muscle contraction.) If any of these proteins is missing because the gene for it is flawed, the membrane probably loses some of its "shock absorber" qualities and has a harder time protecting the muscle cell from injury during normal contraction and relaxation cycles.

In LGMD, the muscle membrane also may be "leaky," letting substances in or out that are supposed to stay on one side of the membrane or the other. Membrane proteins, when they're made correctly and are in their normal positions, may also perform other essential functions in the cell; these functions may be defective when one or more of the proteins are absent.

Not all of the muscle proteins associated with LGMD are in the membrane, however. For instance, calpain-3 is probably located in the main part of the muscle cell, and myotilin and telethonin are located in the part of the muscle cell that allows it to contract and relax.

The types of LGMD are generally classified by letters and numbers that indicate which gene is known or suspected to be involved and whether the disorder is inherited as a dominant or recessive condition, meaning whether one or two flawed genes are needed to cause it. (See "Does It Run in the Family?" page 8.) Some physicians classify LGMD according to which protein is missing or deficient, if this is known. For example, one form may be called



LGMD primarily affects the muscles around the hips and shoulders.

alpha-sarcoglycan deficiency, and another is known as *beta-sarcoglycan deficiency*. In the future, the term *limb-girdle muscular dystrophy* may become obsolete and be replaced by more specific terms.

certainly, although knowing the genetic mutation underlying your disease can be helpful.

What happens along the way?

Often, people with LGMD first notice a problem when they begin to walk with a “waddling” gait because of weakness of the hip and leg muscles. They may have trouble getting out of chairs, rising from a toilet seat or climbing stairs.

Weakness in the shoulder area may make reaching over the head, holding the arms outstretched or carrying heavy objects difficult. It may become increasingly hard to keep the arms above the head for such activities as

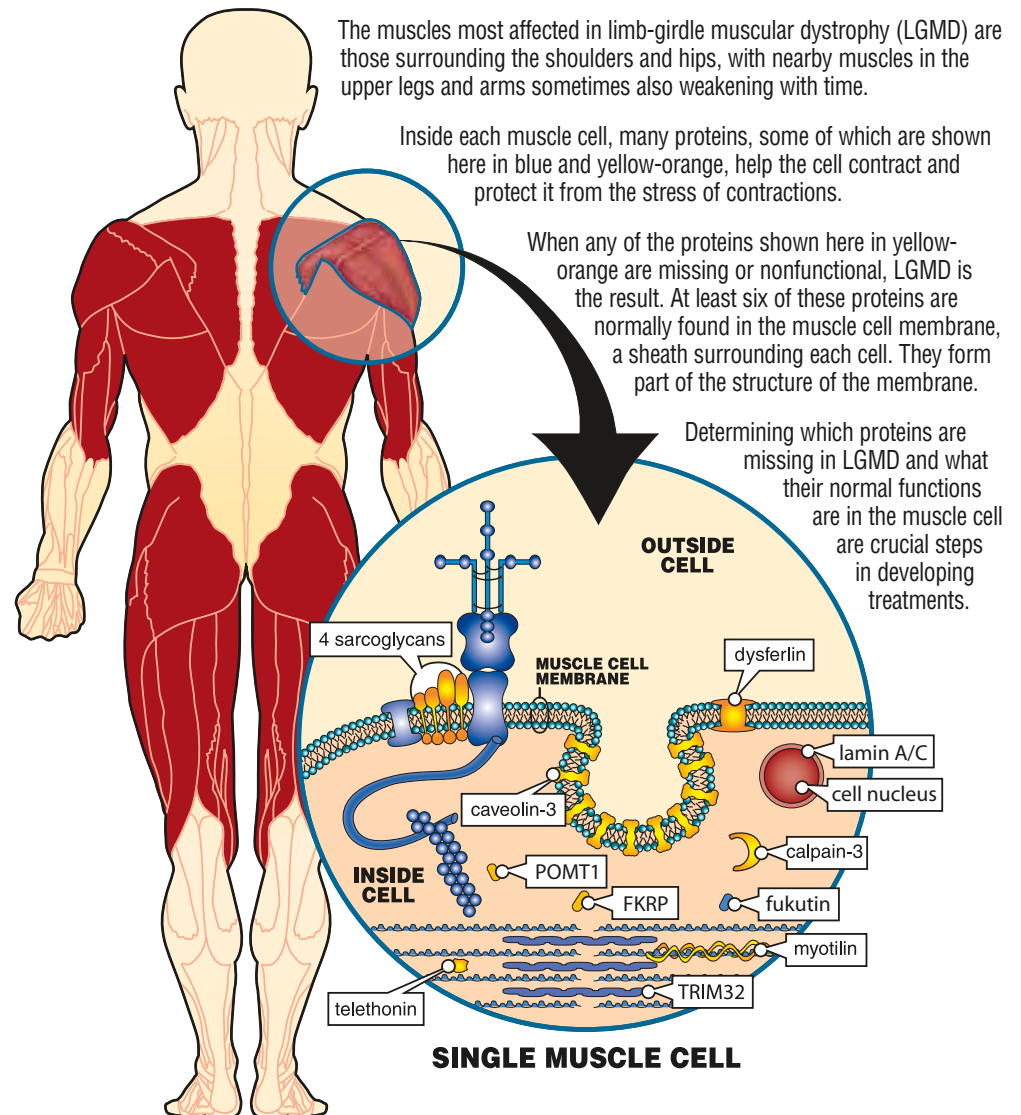
How fast does LGMD progress?

It's not yet possible to predict the course of LGMD in an individual.

Some forms of the disorder progress to loss of walking ability within a few years and cause serious disability, while others progress very slowly over many years and cause minimal disability. At this time, progression in each type of LGMD can't be predicted with



Eventual loss of walking ability is common in LGMD, but some people walk longer than others.



combing your hair or arranging things on a high shelf. Some people find it harder to type on a computer or other keyboard and may even have trouble feeding themselves.

Assistive devices, such as a cane or a long-handled reacher, can make things easier as weakness progresses.

A power wheelchair or scooter becomes convenient when weakness in the pelvic girdle and upper legs causes frequent falls. People whose LGMD has reached this stage often find that a great deal of their independence returns, and they're much less fatigued, when they begin using this type of vehicle.

The heart can be affected in LGMD, but this doesn't occur as often as it does in some other forms of muscular dystrophy. Heart problems can take two forms — weakness of the heart muscle (*cardiomyopathy*) and abnormal transmission of signals that regulate the heartbeat (*conduction abnormalities* or *arrhythmias*). The heart should be monitored for these complications. When necessary, medications or devices (such as pacemakers) can be used to treat them.

Respiratory (breathing) function can decline over time, and this, too, should be monitored regularly. There are devices that can help sustain respiratory function.

What's *not* affected in LGMD?

LGMD, like other muscular dystrophies, is primarily a disorder of voluntary muscles. These are the muscles you use to move the limbs, neck, trunk and other parts of the body that are under voluntary control.

The *involuntary* muscles, except for the heart (which is a special type of involuntary muscle), aren't affected in LGMD.

Digestion, bowel and bladder functions and sexual function, which are carried out by involuntary muscles, remain normal.

Severe pain isn't a major part of LGMD, although limited mobility sometimes leads to

muscle soreness and aching joints. Exercises to keep joints limber, moving around as much as possible, warm baths and, if needed, medication can keep this kind of discomfort to a minimum.

The brain, the intellect and the senses are unaffected in LGMD. People with LGMD can think, see, hear and feel sensations as well as those without muscular dystrophy.

What tests are used to diagnose LGMD?

In diagnosing any form of muscular dystrophy, a doctor usually begins by taking a patient and family history and performing a physical examination. Much can be learned from these, including the pattern of weakness. The history and physical go a long way toward making the diagnosis, even before any laboratory tests are done.

The doctor also wants to determine whether the patient's weakness results from a problem in the muscles themselves or in the nerves that control them. Problems with muscle-controlling nerves, or *motor nerves*, originating in the spinal cord and reaching out to all the muscles, can cause weakness that looks like a muscle problem but really isn't.

Usually, the origin of the weakness can be pinpointed by a physical exam. Occasionally, special testing called *electromyography* is done. In this kind of test, the electrical activity of the muscles is measured and nerves stimulated to see where the problem lies. Electromyography is uncomfortable but not usually very painful.

A *nerve conduction study* also may be done. This too is uncomfortable, but not seriously painful.

Early in the diagnostic process, doctors often order a special blood test called a *CK level*. CK stands for *creatine kinase*, an enzyme that leaks out of damaged muscle. When elevated CK levels are found in a blood sample, it



A wheelchair or scooter, such as the one this physician with LGMD uses, becomes convenient when weakness in the pelvic girdle and upper legs causes frequent falls.



LGMD doesn't impair the intellect, the senses or the desire for a challenge.



An echocardiogram (ultrasound imaging of the heart) can be used to monitor heart function in LGMD.



The diagnostic process usually begins with a history and physical examination.

usually means muscle is being destroyed by some abnormal process, such as a muscular dystrophy or inflammation. Therefore, a high CK level suggests that the muscles themselves are the likely cause of the weakness, but it doesn't tell exactly what the muscle disorder might be.

Today, DNA testing to look for genetic flaws that are known to cause LGMD is available for several forms of the disease and is rapidly expanding. If a particular type of LGMD is suspected, DNA testing, using a blood sample, may be undertaken relatively early in the diagnostic process, often before the doctor considers a more invasive procedure.

In some cases it is necessary for a doctor to order a muscle *biopsy*, the surgical removal of a small sample of muscle from the patient. By examining this sample, doctors can tell a great deal about what's actually happening inside the muscles. Using a variety of techniques, muscular dystrophies can be distinguished from inflammatory and other disorders. Specific testing of the biopsy also may distinguish among different forms of muscular dystrophy.

Tests on the biopsy sample also can provide information about which muscle proteins are present in the muscle cells, and whether they're present in the normal amounts and in the right locations. This can tell the doctor and patient what's wrong with the cells' proteins and provide likely candidates as to which genes are responsible for the problem. The correlation between missing proteins on the muscle biopsy and genetic flaws isn't perfect, however.

Is it important to find out what genetic type of LGMD a person has?

At this time, genetic testing to determine an individual's exact type of LGMD is commercially available for only some LGMD forms. If there are clues as to what gene is involved (from previously tested family members,

biopsy findings or symptoms clearly associated with one or two types of LGMD), it may be practical to do DNA testing to pinpoint the gene defect. However, if there are no such clues, testing for more than a dozen genetic defects is available but extremely expensive.

Understanding your inheritance pattern may, however, be important for family planning. Your family history can help determine the inheritance pattern of your disorder.

Treatment for LGMD, mainly involving physical and occupational therapy, assistive devices, and monitoring for heart and breathing complications, is essentially the same in all forms of the disease. An individual's precise genetic defect makes little difference in these interventions.

Can special diets help in LGMD?

At this time, no special dietary restrictions or additions are known to help in LGMD.

Many people, when they hear the words "lack of a protein," logically ask, "Should I eat more protein?" Unfortunately, eating more protein than your normal requirement has no effect on any of the proteins missing in LGMD. It's true that when you eat a steak, you're ingesting many muscle proteins (from the cow). Your body then breaks down these proteins into their component parts and uses them to build its own proteins. But a person who lacks the genetic instructions to make these new proteins won't be able to make them no matter how much protein he eats.

A doctor may advise a weight reduction or weight stabilization diet for some people with LGMD. Being markedly overweight puts greater stress on already weakened muscles.

Are there special exercises that can help?

A *physical therapy* program is usually part of the treatment for LGMD. Your MDA clinic physician may refer you to the physical

therapy department at your medical center for a thorough evaluation and an individualized exercise program.

The primary goals of physical therapy are to allow greater motion in the joints and to prevent *contractures* (freezing of the joints). These problems can arise when movement is limited, and it's important for the patient's comfort and function to avoid them.

Doctors and therapists have somewhat different opinions on the relative value or danger of various exercise regimens in people with muscular dystrophy. In LGMD, certain kinds of stress-causing exercises may actually hasten muscle damage.

Some experts recommend swimming and water exercises as a good way to keep mus-

cles as toned as possible without causing undue stress on them. The buoyancy of the water helps protect against certain kinds of muscle strain and injury. Before undertaking an exercise program, make sure you've had a cardiac evaluation. And don't swim alone.

Occupational therapy focuses more on specific activities and functions, particularly use of the hands, while physical therapy emphasizes mobility and (where possible) strengthening of large muscle groups. Your MDA clinic also can refer you to the occupational therapy department, where you can receive help with tasks related to your job, recreation or daily living. For example, arm supports can make tasks such as using a computer or fixing your hair less tiring.



Some experts recommend swimming and water exercises to keep muscles toned.



An important goal of physical therapy is to allow greater motion in the joints.

Known Forms of Limb-Girdle Muscular Dystrophy

| Type | Pattern of Inheritance | Gene or Chromosome |
|--------|------------------------|------------------------|
| LGMD1A | Autosomal dominant | Myotilin gene |
| LGMD1B | Autosomal dominant | Lamin A/C gene |
| LGMD1C | Autosomal dominant | Caveolin gene |
| LGMD1D | Autosomal dominant | Chromosome 7 |
| LGMD1E | Autosomal dominant | Chromosome 6 |
| LGMD1F | Autosomal dominant | Chromosome 7 |
| LGMD1G | Autosomal dominant | Chromosome 4 |
| LGMD2A | Autosomal recessive | Calpain-3 gene |
| LGMD2B | Autosomal recessive | Dysferlin gene |
| LGMD2C | Autosomal recessive | Gamma-sarcoglycan gene |
| LGMD2D | Autosomal recessive | Alpha-sarcoglycan gene |
| LGMD2E | Autosomal recessive | Beta-sarcoglycan gene |
| LGMD2F | Autosomal recessive | Delta-sarcoglycan gene |
| LGMD2G | Autosomal recessive | Telethonin gene |
| LGMD2H | Autosomal recessive | TRIM32 |
| LGMD2I | Autosomal recessive | FKRP gene |
| LGMD2J | Autosomal recessive | Titin gene |
| LGMD2K | Autosomal recessive | POMT1 gene |
| LGMD2L | Autosomal recessive | Fukutin gene |

These forms of LGMD have been identified since the early 1990s. More forms will undoubtedly be discovered as research continues.

LGMD *can* run in a family, even if only one person in the biological family has it.

Does It Run in the Family?

On being told they have a genetic disorder such as LGMD, bewildered patients often ask, “But it doesn’t run in the family, so how could it be genetic?”

LGMD *can* run in a family, even if only one person in the biological family has it. This is because of the ways in which genetic diseases are inherited.

LGMD can be inherited in one of two basic ways, known as the *autosomal dominant pattern* and the *autosomal recessive pattern*. “Known Forms of LGMD” on page 7 shows which types follow each pattern.

The word *autosomal* means that the genes involved aren’t on the X or Y chromosome and, therefore, don’t have a preference for either men or women.

In diseases with *dominant* inheritance patterns, a person who inherits a flawed gene from one parent will have disease symptoms. That parent would also have the disease.

In diseases with *recessive* inheritance, a person must inherit two flawed genes — one from each parent — to have disease symptoms. The parents don’t have symptoms.

A recessive form of LGMD can show up in one person when there’s no family history. Other family members may have been *carriers*, having no disease symptoms. Carriers have the genetic flaw (*mutation*) on a chromosome and can have a child with the disease, but *only* if the child’s other parent is also a carrier. So it isn’t unusual for carriers of a rare recessive disease not to know they’re carriers until someone in the family develops the disease.

Just to make things a little more complicated, a person with LGMD may have a brand new genetic mutation (after all, they

have to start somewhere), so there may really be no family history or even carriers of the disorder in the family. However, once someone develops a genetic disease, even if the mutation is *spontaneous* (new) with that person, he or she can then pass on the mutation to any offspring, thereby introducing the gene for the disease into the family.

The details of inheritance risks for any particular form of LGMD depend on many circumstances, including exactly which type of LGMD has been diagnosed. A good way to find out more is to talk to your MDA clinic physician or ask to see the genetic counselor at the MDA clinic. You also can read MDA’s booklet “Facts About Genetics and Neuromuscular Diseases.”

MDA's Search for Treatments and Cures

The MDA website is constantly updated with the latest information about the neuromuscular diseases in its program. See the latest research news at www.mda.org.

Throughout the 1990s and the first decade of the 21st century, MDA-supported researchers identified dozens of genes that, when defective, cause LGMD.

This gene identification work continues to the present day, along with research to determine the precise function of these genes so that missing functions can be compensated for and toxic functions can be inhibited.

In the recessive forms of LGMD, it may be possible to insert a new gene to compensate for one that isn't working properly. This type of intervention — gene therapy — has shown promise in a pilot trial in people with the alpha-sarcoglycan-deficient form of LGMD.

In the dominant forms of LGMD, blocking a toxic function using strategies such as “antisense,” which keep cells from interpreting genetic information, may become a treatment in the future.

Some genetic mutations, known as “premature stop codons,” cause cells to stop reading genetic instructions before a fully functional protein has been synthesized. A drug that causes cells to “read through” these stop codons is being tested in another form of muscular dystrophy (Duchenne) and may have some application in LGMD.

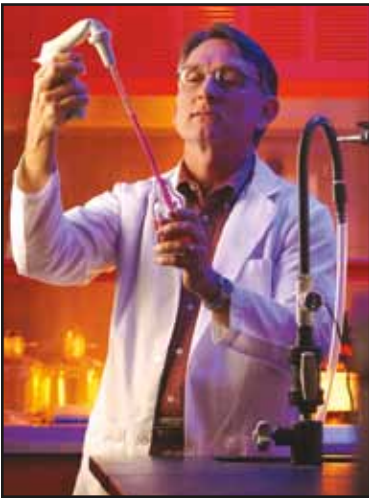
Some genetic mutations add or remove DNA and change the way cells interpret the information in a gene. In Duchenne muscular dystrophy, clinical trials are under way of compounds that coax cells to snip out these error-containing DNA

regions (“exon skipping”); this research also may have relevance for LGMD treatment.

Another avenue of investigation is blocking a natural protein called myostatin, which puts a brake on muscle growth. This strategy has the potential to treat a variety of conditions in which muscle growth or maintenance is insufficient.

Still another strategy is to use stem cells to help ailing muscles regain strength. Stem cells are early-stage, flexible cells that can give rise to mature muscle fibers. They're found in muscle tissue and other places in the body, and scientists are working to determine which cells are the safest and most effective to test in people with LGMD and other diseases.

MDA-supported researchers worldwide continue to pursue every avenue that might lead to potential treatments for LGMD.



MDA Is Here to Help You

The Muscular Dystrophy Association offers a vast array of services to help you and your family deal with LGMD. The staff at your local MDA office is there to assist you in many ways. The Association's services include:

- nationwide network of clinics staffed by top neuromuscular disease specialists
- MDA summer camps for kids with neuromuscular diseases
- help with locating durable medical equipment through its national equipment program
- financial assistance with repairs or modifications to all types of durable medical equipment
- annual occupational, physical, respiratory or speech therapy consultations
- annual flu shots
- support groups for those affected, spouses, parents or other caregivers
- online support services through the e-community *myMDA* and through *myMuscleTeam*, a program that helps recruit and coordinate in-home help

MDA's public health education program helps you stay abreast of research news, medical findings and disability information through magazines, publications, educational speakers, seminars, videos and newsletters.

MDA's website at www.mda.org contains thousands of pages of valuable information, including disease specifics, research findings, clinical trials and past magazine articles.

Everyone registered with MDA automatically receives *Quest*, MDA's award-winning quarterly magazine. *Quest* publishes detailed articles about research findings, medical and day-to-day care, helpful products and devices, social and family issues, and much more. Other MDA publications can be found at www.mda.org/publications; many booklets are available in Spanish. Ask your local office for "MDA Services for the Individual, Family and Community" and for help with obtaining copies of other publications.

If you have any questions about LGMD, someone at MDA will help you find the answer. To reach your local MDA office, call (800) 572-1717.



On the cover:
Amy was found to have limb-girdle MD at age 8 and began using a wheelchair in her teens. Now married, she teaches high school Spanish and has been nationally honored for her teaching and as the 2003 recipient of the MDA National Personal Achievement Award.

MDA's Purpose and Programs

The Muscular Dystrophy Association fights neuromuscular diseases through an unparalleled worldwide research effort. The following diseases are included in MDA's program:

Muscular Dystrophies

Myotonic dystrophy (*Steinert disease*)
Duchenne muscular dystrophy
Becker muscular dystrophy
Limb-girdle muscular dystrophy
Facioscapulohumeral muscular dystrophy
Congenital muscular dystrophy
Oculopharyngeal muscular dystrophy
Distal muscular dystrophy
Emery-Dreifuss muscular dystrophy

Motor Neuron Diseases

Amyotrophic lateral sclerosis (*ALS*)
Infantile progressive spinal muscular atrophy
(*Type 1, Werdnig-Hoffmann disease*)
Intermediate spinal muscular atrophy
(*Type 2*)
Juvenile spinal muscular atrophy
(*Type 3, Kugelberg-Welander disease*)
Adult spinal muscular atrophy (*Type 4*)
Spinal-bulbar muscular atrophy
(*Kennedy disease*)

Inflammatory Myopathies

Polymyositis
Dermatomyositis
Inclusion-body myositis

Diseases of Neuromuscular Junction

Myasthenia gravis
Lambert-Eaton (myasthenic) syndrome
Congenital myasthenic syndromes

Diseases of Peripheral Nerve

Charcot-Marie-Tooth disease
Friedreich's ataxia
Dejerine-Sottas disease

Metabolic Diseases of Muscle

Phosphorylase deficiency (*McArdle disease*)
Acid maltase deficiency (*Pompe disease*)
Phosphofructokinase deficiency
(*Tarui disease*)
Debrancher enzyme deficiency
(*Cori or Forbes disease*)
Mitochondrial myopathy
Carnitine deficiency
Carnitine palmityl transferase deficiency
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Myoadenylate deaminase deficiency

Myopathies Due to Endocrine Abnormalities

Hyperthyroid myopathy
Hypothyroid myopathy

Other Myopathies

Myotonia congenita
Paramyotonia congenita
Central core disease
Nemaline myopathy
Myotubular myopathy
Periodic paralysis



MDA's website, mda.org, is constantly updated with the latest research news and information about the diseases in its program. Follow MDA on Facebook, Twitter and YouTube.



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